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DIFFICULTIES IN THE DIFFERENTIAL DIAGNOSIS OF BRONCHOGENIC CARCINOMA

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IN RECENT years the increasing interest in carcinoma of the lung has led to much improvement in the diagnosis of pulmonary tumors. With an ever better roentgen technique and by bronchoscopy their differentiation from other involvements of the lungs seems to have become comparatively easy and a diminishing number of patients with endobronchial cancer die because of an erroneous diagnosis. However, with mounting experience in the many clinical and pathologic variations of such tumors, and especially with the growing desire for their early discovery, it becomes apparent that a considerable number cannot be definitely recognized by the conservative diagnostic methods. Large scale routine x-ray examinations of the chest are beginning to provide us with increasing numbers of small findings, doubtful as to their significance and origin. When, after the war, as we hope, x-ray examinations of supposedly healthy individuals will become universal, there may emerge a preponderance of such lesions over the advanced ones which are mostly being seen now.

Routine chest fluoroscopy of all patients of the outpatient department of the University of Chicago Clinics was intended and is carried out chiefly as a case-finding program for tuberculosis, but has proved most helpful in the discovery of nontuberculous involvements of the chest. So much so, in fact, that we would think the procedure

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justified for the sole purpose of uncovering cardiovascular disease and tumor involvements. Of 15,000 patients, 91 or $\frac{6}{10}$ of 1 per cent were found to have intrathoracic neoplasms. Table I shows the differentiation of the total number found into various types of tumors. Over one-third were classified as metastatic growths, and more than one-fourth of the total were subsequently diagnosed as primary bronchogenic carcinoma. It is interesting to note that about one-half of all the patients with neoplasms were assigned to special clinics in our institution where physical examinations which could be expected to lead to the diagnosis are not carried out. The question of physical findings, however, seems altogether irrelevant, since none whatsoever are elicited in the overwhelming majority of patients with early tumors. The complaints which caused the patients to seek medical care were in many cases entirely unrelated to the chest findings. Among hospitalized patients also, pulmonary tumors have been found which could not be connected with the patient's case history. Often the diagnosis has been due to no other fact but that our attending and house staffs, during the past decade, have become more and more conscious of the benefits of x-ray examination of the chest in any case.

TABLE I

FINDINGS OF INTRATHORACIC TUMORS IN 15,000 PATIENTS ROUTINE CHEST FLUOROSCOPY IN THE OUTPATIENT DEPARTMENT, UNIVERSITY OF CHICAGO CLINICS

TYPE OF TUMOR	NO.	PER CENT OF PATIENTS EXAMINED	PER CENT OF TUMORS FOUND
Metastatic carcinoma	34	0.23	37.3
Primary carcinoma	25	0.17	27.4
Lymphoma	19	0.13	21.0
Sarcoma	5	0.03	14.3
Undiagnosed	5	0.03	
Miscellaneous	3	0.02	
Dermoid cyst			
Neurofibroma			
Hemangioma			
Totals	91	0.61	100

The experience that growing numbers of patients are being saved by improved surgical techniques has shouldered physicians with new diagnostic responsibilities toward tumors of the lung. This paper is offered as a plea for early diagnosis and for the exploitation of all available diagnostic methods as soon as suspicious lesions are discovered. That the diagnosis may be difficult even in more advanced involvements is shown by some of the cases which are presented. They have reminded us vividly that x-ray examination, which is indispensable for the discovery of a lesion, in no case offers a reliable differential diagnosis. They also demonstrate the frequent failure of bronchoscopy, or rather bronchobiopsy, the only conservative method which can result in diagnostic proof when the tumor is accessible to the instrument.

Like tuberculosis the really early carcinoma, if it does not involve the larger bronchial elements, is not likely to produce symptoms for a considerable time, or such mild and seemingly insignificant symptoms that they are disregarded by the patient. The roentgen evidence sometimes is hard to differentiate from small tuberculous or nontuberculous inflammatory lesions. Bronchoscopy in these early peripheral tumors which, according to Jaffe,[1] constitute 13 per cent of the total incidence will always be negative. The prediagnostic history of the following cases should be illustrative of the seeming insignificance and obscurity of early carcinoma and of some problems in more advanced lesions, especially when they are complicated by unrelated disease.

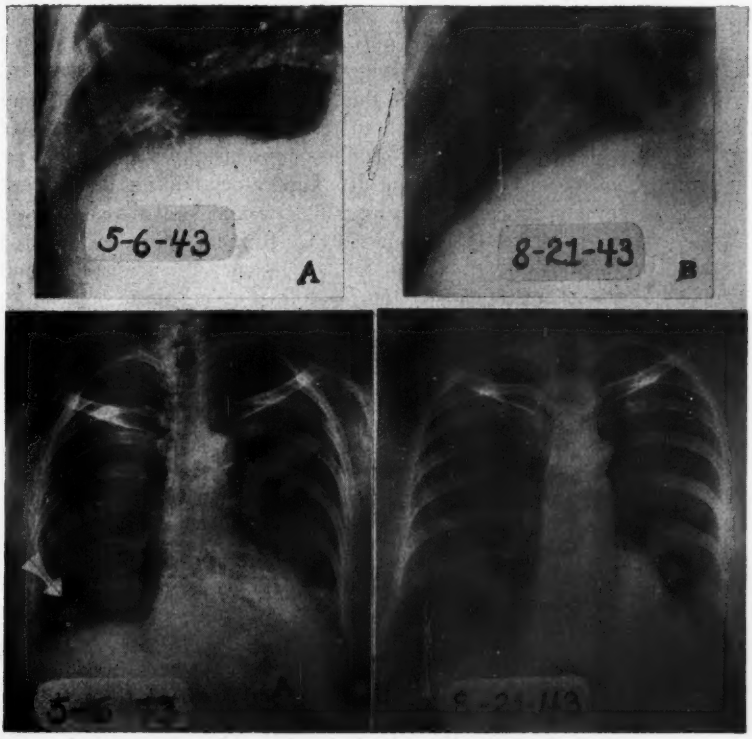

Fig. 1.

CASE 1 (Fig. 1, Unit No. 240063, X-ray No. 82179).—B. C. W., aged 65 years, was a white housewife. The patient was admitted to the Clinics in April, 1940, with complaints of gastric distress, nervousness, and other rather vague symptoms. Diabetes had been suspected by a private physician but was not verified in the Clinic. Some of the symptoms, if not all of them, were suggestive of functional origin. Examinations of the gastrointestinal tract were negative. In the course of

routine examinations an x-ray diagnosis of maxillary sinusitis was made. Otherwise the case was diagnosed as one of functional bowel distress. There was no reason to change that diagnosis on return visits in January and February, 1942. The patient was re-examined in May, 1943, when she complained of pain in the right lower quadrant and other abdominal symptoms. On routine chest fluoroscopy (which had been introduced eight months before) a small infiltrate was noticed in the right lower lung field and verified by roentgenograms (Fig. 1*A*). The possibility of primary or metastatic neoplasm occurred at the time, but the ill-defined small lesion was considered doubtful and kept under observation. In August, 1943, the roentgenogram showed it somewhat increased in size, it was better circumscribed, of more hemogenous density, and by then seemed highly suggestive of a growing tumor (Fig. 1*B*). There still were no symptoms indicative of pulmonary involvement, although in retrospect the patient now stated that she had had frequent colds during the three previous years. In view of her having omitted this complaint before, the symptoms apparently had been mild and due to the sinus involvement. Laboratory findings were either negative or of no clinical significance. The weight had increased from 52.2 to 57.5 kg. between 1940 and 1943. Bronchoscopy was omitted because of the peripheral location of the lesion. Its persistence and slowly increasing size enhanced the possibility of neoplasm sufficiently to ascertain the diagnosis by surgical exploration. A hard mass 2½ by 3 cm. in size was found in the right lower lobe. The histologic examination showed adenocarcinoma.

This case then stands out as an example of early carcinoma discovered by routine x-ray examination in a patient presenting herself with symptoms wholly unrelated to her most important disease. The small involvement found on first roentgen observation differed in none of its aspects from early inflammatory lesions, especially not from many of those which at the time of this observation occurred in almost epidemic multiplicity and which have become known under the term of atypical or virus pneumonia.

Case 2 (Fig. 2, Unit No. 172703, X-ray No. 55669).—O. C. M., aged 60 years, was a white salesman. The patient had been suffering from asthma, apparently due to ragweed pollen allergy from childhood until the age of 20, when the attacks ceased. They reappeared at the age of 42 again with hay fever and were troubling him increasingly ever since. He was first seen and hospitalized in 1937. The symptoms were what appeared to be genuine asthmatic attacks with cough and mucopurulent expectoration and with chronic dyspnea. The roentgenogram showed the lung fields clear of infiltrations (Fig. 2*A*). The diagnosis was chronic maxillary sinusitis, bronchial asthma, and bilateral emphysema with possible bronchiectasis. The asthmatic symptoms were relieved by adrenalin and frequent drainage of the infected sinuses.

After clinic treatment in the interval there was a second short period of hospitalization in August, 1938, for the same complaints. Chest roentgenograms then showed a small infiltrate in the subapical area of the right lung field (Fig. 2*B*). Since other similar areas, especially in the left lower lobe, by their disappearance proved to have been the result of bronchial aspiration and of inflammatory character, the lesion in the right upper lobe was first assumed to be of the same etiology. On re-examination in January, 1939 (Fig. 2*C*), it was found to have persisted and was suspected as neoplasm while the other patchy areas had cleared. The cut out films in Fig. 2 show the slow development into a tumor of apple size by April, 1941. There were no extrapulmonary findings. Sputum tests were negative for acid-fast bacilli. Other laboratory findings were insignificant. The weight increased from 53.6 to 63 kg. between 1937 and 1941. The severe pulmonary symptoms contraindicated bronchoscopy, especially since the peripheral location of the lesion made positive findings unlikely. Surgical exploration followed by lobectomy was performed after the patient's family had been advised of the precariousness of the operation caused by the prevailing complications. The histologic examination revealed a squamous-cell carcinoma containing areas of necrosis.

The severe bronchial symptoms of long standing in this patient suggested the possibility of a small bronchopneumonia on the site of the carcinoma especially since the lesion, after wholly negative x-ray observations, originated simultaneously with other similar areas which proved to be of inflammatory character. Again in this case the discovery of the neoplasm was incidental to x-ray examination of the chest which, although not a routine test, was carried out in the follow-up of a previously diagnosed and unrelated bronchial condition.

CASE 3 (Fig. 3, Unit No. 308221, X-ray No. 111461).—A. J. H., aged 45 years, was a white laborer. The patient had no complaints except for fairly frequent upper respiratory infections during the past ten years. He was first examined in the Clinic in April, 1943, because a pulmonary lesion was discovered on routine x-ray examination to which he was subjected as a prospective employee of the University. In September, 1942, an x-ray examination of the chest had been made on induction to the Army. This earlier roentgenogram (Fig. 3*A*) was obtained from the patient's Draft Board. It showed a small diffuse focus identical to the many early tuberculous lesions which are now being found in case-finding surveys. It probably played an important role in the patient's rejection from Army Service although he claimed that the reasons were defective eyesight and teeth. Physical examination in our Clinic was entirely negative. Roentgenograms of the chest (Fig. 3*B*) showed a small circumscribed infiltrate in the right lower lobe with a suggestion of beginning excavation; it was suspected as tuberculosis and kept under close observation. Re-examination six weeks after the

4-5-37
A
8-1-38
B
1-12-39
8-1-38
1-12-39
4-28-39
12-11-39
4-16-40
7-5-40
12-12-40
4-10-41

Fig. 2.

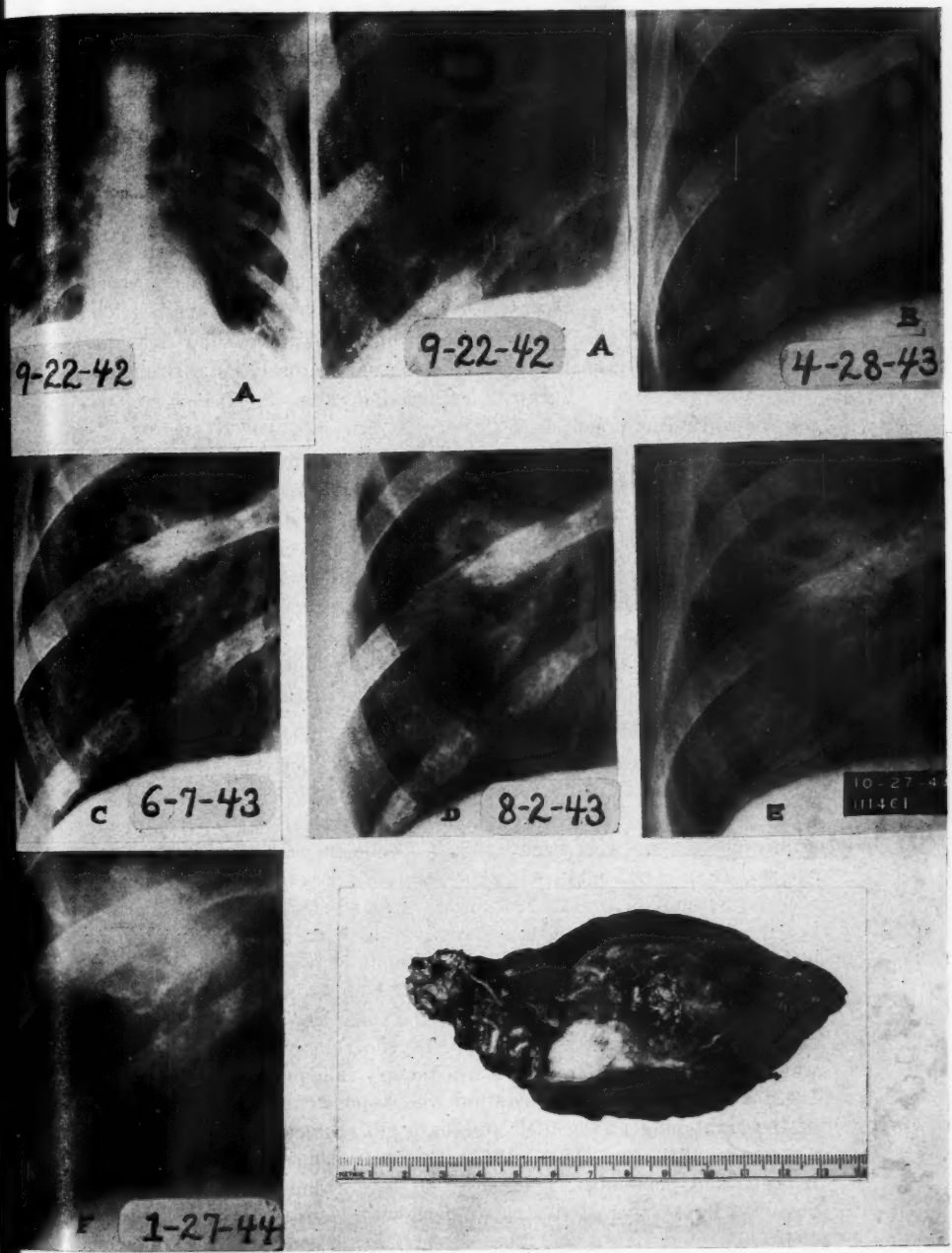

Fig. 3.

first visit to our Clinic revealed definite excavation (Fig. 3*C*). This strengthened the impression of tuberculosis. Subsequent roentgenograms shows extension of the total involvement as well as of the cavity along the lines on which a tuberculous lesion of this initial appearance may be expected to develop (Fig. 3, cut-out films). However, numerous sputum tests, including some by gastric lavage and guinea pig inoculation, were negative for acid-fast bacilli. Other laboratory findings were insignificant. The blood sedimentation rate was 4 and 9 mm. after thirty and sixty minutes, respectively (Cutler). Nontuberculous diseases such as pneumonitis and lung abscess were thought of but appeared unlikely in the absence of any recent history or symptoms of infection. In January, 1944, the possibility of neoplasm was considered as the strongest one. A bronchogram added no new information. Bronchoscopy was negative. Surgical exploration Feb. 8, 1944, revealed squamous-cell carcinoma.

The development of the neoplasm in this case closely resembled that of minimal exudative caseous tuberculosis with early excavation. The disappearance of the cavity in the more advanced stages of the involvement is a frequent occurrence in tuberculosis, but certainly not typical for only that disease. While in infectious processes it is due to the filling in of the cavity with caseous or purulent material or to an obscuring effect of a new perifocal infiltration, it seems that in tumor involvements it is mostly caused by newly developed atelectasis. Case 4 demonstrates a very similar sequence of observations.

Case 4 (Fig. 4, Unit No. 320031, X-ray No. 115942).—A. B. P., aged 44 years, was a negro housewife. This patient's left breast was amputated for carcinoma in July, 1939. In January, 1940, her tonsils were removed because of recurrent upper respiratory infection. Roentgenograms of the chest were negative then. Following the tonsillectomy she suffered from cough and some expectoration for several months. Chest roentgenograms in August, 1940, were reported as showing some density in the right lung field, but on re-examination of the films this now seems questionable. There was no definite change shown on two subsequent roentgen examinations during 1941 (Fig. 4*A*) but an increase of bronchovascular markings especially in the right subapical area seemed to warrant further observation. (These roentgenograms were taken on paper which somewhat interfered with satisfactory interpretation.) In April, 1942, a definite area of infiltration was demonstrable at the periphery of the right lung at the fifth and sixth rib posteriorly (Fig. 4*B*). In November, 1942, and April, 1943, there was definite excavation which in June and September, 1943 (Fig. 4*C* to *F*), had either filled or was obscured by an increased area of peripheral density. From January, 1940, until February, 1943, the patient had no complaints. Following that period she had some pain in the right side of her chest and an

attack of rheumatism in both knees. The patient's private physician was treating her for tuberculosis by conservative methods. Sputum tests were negative for acid-fast bacilli. In September, 1943, he suspected a lung abscess and referred the patient to Provident Hospital for further study. There again sputum tests were negative and other laboratory findings unimportant. There had been no significant loss

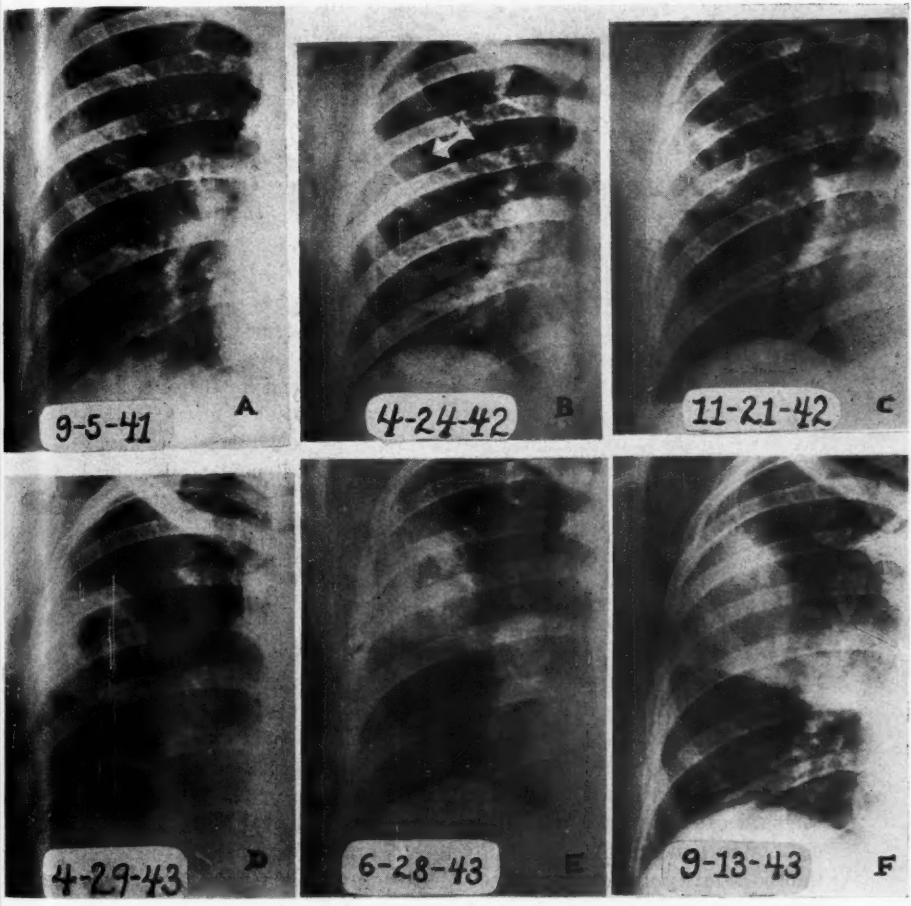

Fig. 4.

of weight. A two-stage operation for drainage of the abscess was performed. Histologic examination of the abscessed wall revealed a poorly differentiated squamous-cell carcinoma.

There were four diagnostic possibilities in this case. One was that of a metastatic neoplasm following carcinoma of the breast. In view of the tonsillectomy with subsequent chronic pulmonary symptoms a

chronic lung abscess was eventually considered by the attending physician. However, the appearance of the first roentgen findings more than two years after the operation would make this unlikely. For the greater part of the duration of the disease the patient was treated for tuberculosis apparently because of the chronicity of the lesion but chiefly, as in the previous case, because of the development of the lesion through the seemingly typical phases of a tuberculous infection.

In the four patients so far presented, the clinical observations were made beginning with the first appearance of the tumors. Naturally such early developments with minimal x-ray findings present a greater diagnostic problem than the well-grown neoplasms. However, it seems that in general and in x-ray practice even the smallest isolated hemogenous density is not more deceiving than the finding of an excavation. Cavity formation in bronchogenic carcinoma can be an early development, as we have seen. In advanced carcinoma it is quite common. Fishberg and Rubin[2] estimated that excavation is found in one-third of all cases of bronchogenic carcinoma. Hauser and Wolpaw[3] have discussed the various forms of cavity formation and found obstruction of vascular elements and infection as the chief causative factors. They describe the tumor itself and the pulmonary areas which depend for their areation upon obstructed bronchial elements as the two essential locations of such cavities. In the clinical experience of most of us excavation is so closely associated with disease of infectious etiology that it may tend to lead away from the diagnosis of neoplasm. Certainly it increases the difficulties of differential diagnosis as a few additional cases may illustrate.

CASE 5 (Fig. 5, Unit No. 136369, X-ray No. 52531).—W. S., aged 54 years, was a white gardener. The patient was first examined in the Clinic in April, 1940. He complained of pressure sensation in the area of the right parasternal region. Three years before, he had had an attack of pneumonia, and the feeling of tenderness in the right side began about one year after that. For two months previous to examination this symptom increased considerably and he had a slight morning cough with blood-tinged sputum. During the same period a few small tender nodules developed in the skin of the medial side of the right elbow. Physical examination verified the latter and revealed dullness over the right apical pulmonary area. Roentgenograms of the chest (Fig. 5*A*) showed a fairly well circumscribed density in the right apical lung field. Laboratory findings were insignificant except for a moderate increase in white blood cells and an increased blood sedimentation rate to 18 and 22 mm. after thirty and sixty minutes, respectively (Cutler). A bronchogenic tumor was suspected, possibly with skin metastases. However, a biopsy of the nodules on the arm proved them to be lipomas. Bronchoscopy was advised but the patient did not submit to it at that time. He remained under clinical observation while continuing with his work. His weight increased somewhat during that period. He improved

symptomatically. A roentgenogram taken in October, 1940 (Fig. 5*B*), six months after the initial observation, failed to show any change as did fluoroscopy on Jan. 2, 1941. Three weeks later the patient returned because of nausea and vomitus of some blood. His weight had dropped by 2½ kg. during this short period. Roentgenograms (Fig. 5*C*) showed that the right apical lesion was cavernous. All sputum tests including guinea pig inoculation were negative for acid-fast bacilli. The patient now submitted to bronchoscopy which was negative. Clinical and roentgen examination of the gastrointestinal tract revealed an active duodenal ulcer. After the patient's recovery from the acute symptoms, surgical exploration of the right lung was performed in March, 1941. Histologic examination showed squamous-cell carcinoma.

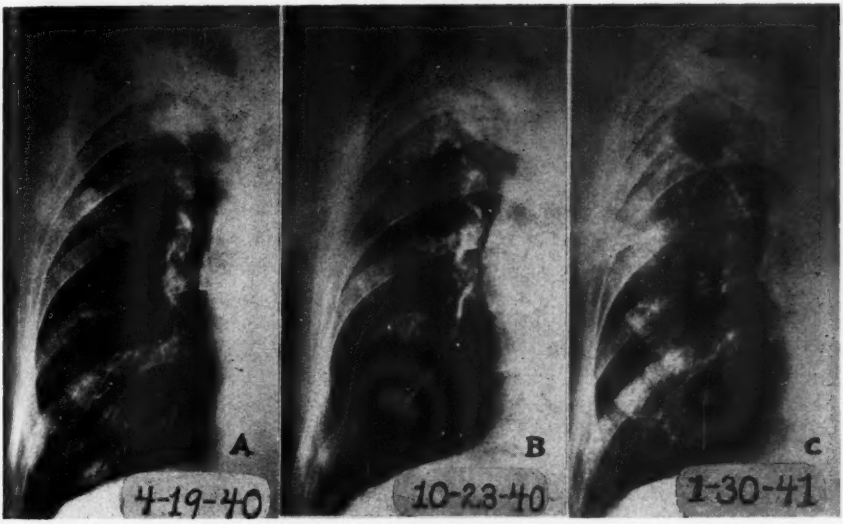

Fig. 5.

In this case the spontaneous drainage of a massive lesion after one year's observation coincidental with gastrointestinal symptoms suggested a caseous tuberculosis expelling its caseous contents, resulting in abundant ingestion of tubercle bacilli. However, the absence of acid-fast organisms from the sputum during obvious aspiration of some of the material into the bronchial system contradicted that impression. The diagnosis of an unrelated duodenal lesion later explained the abdominal complaints. Like the two previously described patients with excavated tumor, we see here that failure to recover acid-fast bacilli by careful and frequent tests should point to the possibility of malignant neoplasm, especially in patients of more advanced age. Progressive excavation in tuberculosis, especially when definite drainage can be followed by serial roentgen observations, should be expected to yield bacilli in the sputum. Case 6 may illustrate this point.

CASE 6 (Fig. 6, Unit No. 261139, X-ray No. 91154).—C. H. F., aged 62 years, was a white housewife. The patient was first admitted in April, 1941. At intervals she had been suffering from a dry, hacking cough for fifteen years but otherwise had been in good health. In 1920 a nonmalignant tumor had been removed from the right breast. During the six months preceding admission, the cough had increased considerably and was accompanied by dyspnea, fullness in the chest, and general malaise. There was no fever. A tumor of the right lung had been diagnosed elsewhere and the patient was referred for therapy. The routine laboratory tests were negative or insignificant. Repeated sputum tests failed to show acid-fast bacilli. Roentgenograms of the chest (Fig. 6*A*) revealed a circumscribed dense area in the right upper lung field which the roentgenologists reported as representing "undoubtedly neoplasm." Bronchoscopy was negative. Surgical exploration revealed a firm, circumscribed mass of about the size of an egg without evidence of glandular involvement in the mediastinum. The operation was extended into removal of the right upper and middle lobes. Pathologic examination showed the mass as a sharply circumscribed tuberculous lesion with a fibroid wall in the center of which a cavity of 3 cm. in diameter contained caseous material (Fig. 6*D*). The histologic diagnosis was tuberculosis. The patient recovered well (Fig. 6*B*) and was discharged less than three weeks after the operation. Some cough persisted but otherwise she was well until June, 1942, when cough and especially expectoration began to increase. There was also a recurrence of fatigue and some dyspnea. The weight had dropped by 8½ kg. against that on the previous admission. Roentgen examination (Fig. 6*C*) revealed a new large isolated mass in the right lung field near the mediastinum. Routine sputum tests were negative for acid-fast bacilli. Bronchoscopy showed purulent discharge from the right main bronchus but no lesion. By February, 1943, roentgenograms of the chest (Fig. 6*D*) demonstrated a fluid level within the lesion signifying drainage into the bronchus. The sputum was then positive for acid-fast bacilli on smears. Further surgical interference was considered but refused by the patient.

Contrary to the other cases, the lesion in this patient with little doubt was taken to be a neoplasm but proved to be a tuberculous involvement of somewhat unusual aspects and course. The initial involvement could not be diagnosed before histologic examination of the removed specimen. The secondary development, the nature of which of course could be construed from the findings in the first, was ascertained as tuberculosis from the sputum findings. It is worth noting, however, that in this lesion too the sputum was negative until spontaneous drainage from it had begun.

Tuberculous cavities which have expelled their essentital caseous content before they are recognized may not yield tubercle bacilli for considerable periods of time and then only in scant numbers. The failure

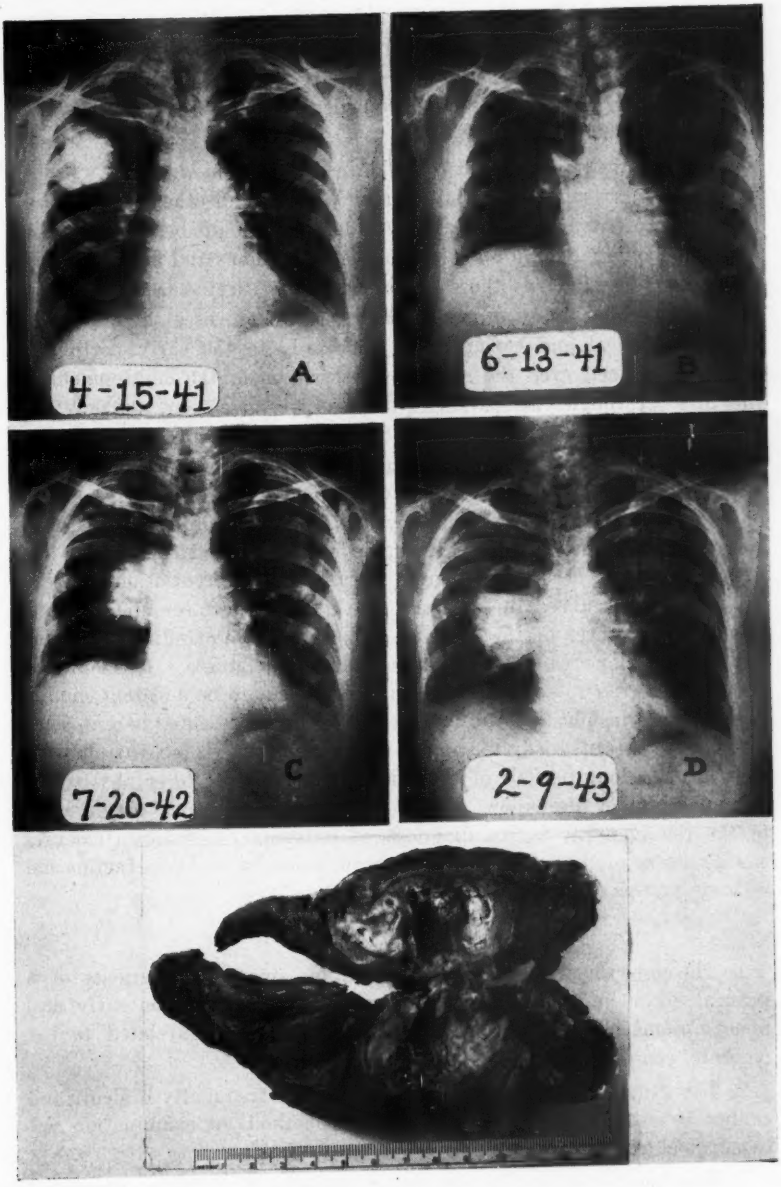

Fig. 6

of such excavations to discharge acid-fast bacilli therefore should not be construed as indicating nontuberculous disease. But when abundant drainage occurs under medical observation and especially when it can be followed by x-ray examination as in the two cases just described, tubercle bacilli should be found in considerable numbers if the questionable lesion is tuberculous.

This is an important point to make in a condition where, as we wish to state in agreement with Hauser and Wolpaw and others, the clinical picture so often fails to reveal anything which could be considered as pathognomonic. An impressive number of symptoms and findings which have been described as those of bronchogenic carcinoma by our own group[4, 5] and by many others in larger series of cases should not be taken as typical and certainly do not apply to the early peripheral tumors. In fact, even the roentgen observation of the development of the tumor through various stages may, as we have seen, not only not assist in better differentiation from inflammatory processes but actually may obscure it by the great resemblance of two or more diseases in each of the various phases of their development and even in the length of time during which each phase develops. We have already stated that roentgen examination, while invaluable in establishing the presence of a lesion, cannot be relied upon to permit the differentiation between neoplasm, tuberculosis, lung abscess, and some of the rarer lung involvements. Therefore, in the absence of bronchoscopic findings, surgical exploration alone can lead to an acceptable diagnosis. It should be undertaken even in early cases when there seems to be a strong enough possibility of neoplasm. The six cases which were presented here in some detail were chosen chiefly to support that contention. The x-ray observation through long periods of their development served to emphasize the difficulties under discussion. Without doubt, as the greatest single value of the roentgen ray in the diagnosis of pulmonary carcinoma emerges the discovery of the early presymptomatic lesion by routine examination of large groups of the population.

SUMMARY AND CONCLUSIONS

1. Through routine roentgen examination among the patients of a general clinic and hospital, bronchogenic carcinoma in the early and nonsymptomatic stage as well as advanced tumors unrelated to the patients' complaints are found in appreciable numbers.

2. The differential diagnosis in early cases is frequently difficult and cannot be established by the conservative methods of examination but by surgical exploration only.

3. Roentgen examination can never establish a definite differential diagnosis even in extensive involvements. Particular diagnostic difficulties are offered by excavated lesions which are not accessible to the bronchoscope.

4. Extrapulmonary involvements and systemic disease frequently confuse the clinical impression and obscure the picture of carcinoma.

5. The absence of tubercle bacilli from the sputum eliminated by excavating lesions is most significant in the diagnosis of neoplasm.

6. A number of cases are described in illustration of the previously mentioned diagnostic difficulties.

7. Emphasis was put on the serial roentgenologic demonstration of the development of bronchogenic carcinoma from its early beginnings.

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(See discussion on page 119.)

BRONCHIAL ADENOMA

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REVIEWING the records of our cases of bronchial tumor and scrutinizing them closely, we have been able to find twenty that we feel may be considered typical of the clinical and pathologic entity most commonly known as benign adenoma of the bronchus. The essential features of these cases are shown in Table I. We feel that there is no need to take time or space to discuss in detail the clinical symptoms, physical signs, and x-ray findings, either with respect to individual cases or in general, because these have already been adequately considered by us,[1, 2] and others. However, it may be worth while to note in passing a few clinical facts. For example, sixteen (or 80 per cent) of our cases were in women, and only four (20 per cent) in men. The age of diagnosis varied from 13 to 44 years, and the majority of cases were diagnosed in the second and third decades. The symptoms were chiefly hemoptysis and cough, often productive. The x-ray was negative in a few instances, but generally showed obstructive atelectasis and occasionally pleural effusion.

Biopsy was done bronchoscopically in all cases, but the tissue was by no means always diagnosed correctly the first time the slide was examined. One of our very interesting work sheets used in preparing this paper was a sheet listing the various histopathologic diagnoses made in each of our cases by various pathologists and on different occasions by the same pathologists.

We believe we have made some progress toward simplifying and standardizing the criteria for diagnosis, and it is this belief, principally, that led us to request a place on this program. The present status of our knowledge of bronchial adenoma from the pathologist's viewpoint is summarized concisely by one of us (F. W. K., pathologist) in the following paragraphs.

PATHOLOGY

Some early descriptions of the pathology of this lesion were concise and rather unequivocal, but the numerous contributions to the literature in recent years, while they have served well to call attention to the existence of such an entity, have tended to cause confusion among pathologists and surgeons alike concerning histologic structure. Generally

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speaking, tumor diagnosis by morphologic characteristics is difficult, but cataloguing the characteristics may make it less so.

Bronchial adenomas show a peculiar epithelial proliferation in an equally peculiar stroma.

The epithelial characteristics are as follows: (1) The cells are cuboidal, sometimes even columnar, arranged as a lining layer in spaces of varying size. Generally these cells form two or more layers, or they may even fill the space entirely. Within the first layer are often polyhedral cells. There may be apparent free cells of irregular outline. The cells are often so closely packed that cytoplasmic outlines are not recognizable. (2) The nuclei are round or oval, and while often light-staining, with delicate chromatin markings, they are frequently subject to pyknotic changes, appearing smaller and staining so deeply that chromatin markings are not distinguishable. As a result of this appear-

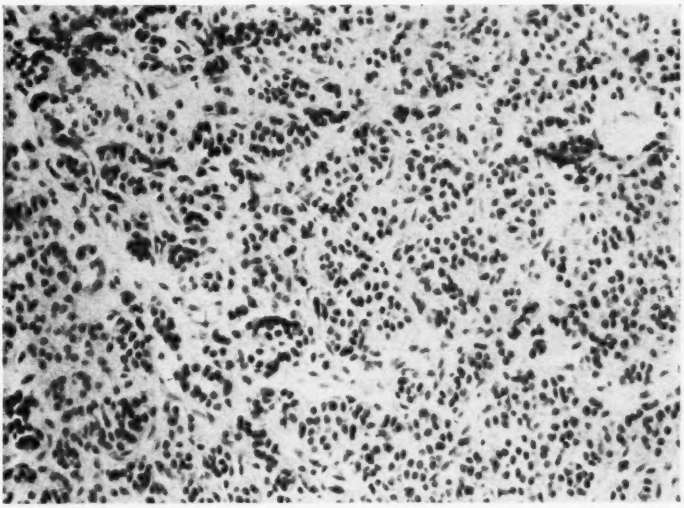


Fig. 1.—Typical picture of bronchial adenoma. Note uniformity of size and shape of nuclei, and absence of clear-cut lumina. Compare with Figs. 2 and 4.

ance, some recent reports compared these cells to lymphocytes, which they most definitely are not. I would say mitoses *never* occur, were it not for a dislike for the word never. I have not been able to find mitoses. (3) The tumor appears to regress sometimes, as is evidenced by density or fibrosis, with shrinkage of the cells and striking pyknosis of nuclei. Nuclei then are oval or spindle shaped, stain a blue black, and are closely packed. (4) Occasionally, in what I think are more rapidly growing tumors, the glandular pattern is not so clear. Definite lining cells are hard to find, the cells lie in compact masses, and cytoplasmic outlines are less distinct. (5) Sometimes papilla-like masses are seen either as solid cords of cells or with the epithelium arranged on either side of a blood

TABLE I

ANALYSIS OF TWENTY CASES OF BRONCHIAL ADENOMA

PATIENT	SEX	AGE	SYMPTOMS	X-RAYS	TREATMENT	RESULT	DURATION (YR.)
B. A.	F	34	Prod. cough 2 yr., hemoptysis 2 yr., "pneumonia"	Atelectasis of left lower lobe	Forceps, electrocoagulation	Symptomatic cure, reaeration	4½
E. B.	F	28	Wheezing 3 yr., prod. cough 2 yr., blood streaking, "pneumonia"	Atelectasis of right lower lobe	Forceps, electrocoagulation	Symptomatic cure, reaeration	6
E. B.	M	21	Prod. cough 8 yr., hemoptysis 5 yr., dyspnea, "pneumonia"	Atelectasis of right middle and lower lobes	Forceps, electrocoagulation	Still under treatment	8½
M. B.	F	15	Cough 2½ yr., "pneumonia" and empyema	Atelectasis of right lower lobe	Lobectomy (January, 1942)	Well	4½
J. B.	M	13	Cough 3 yr., "pneumonia"	Atelectasis of right middle and lower lobes	Forceps, electrocoagulation	Symptomatic cure, reaeration	3½
M. C.	F	24	Hemoptysis 4 yr., cough, occasional pain	Atelectasis of right middle and lower lobes	Forceps, electrocoagulation, x-ray	Symptoms minimal, still under treatment	24
J. C.	F	28	Prod. cough 2 yr., blood streaking, dyspnea	Atelectasis of right lower lobe	Forceps	Symptomatic improvement	2
T. D.	M	42	Hemoptysis 9 mo., cough 9 mo.	Essentially negative	Forceps, electrocoagulation	Symptomatic cure	3¾
P. D.	M	35	Hemoptysis 3 mo., cough 3 mo.	Atelectasis of right upper lobe	Forceps	Partial reaeration, still under treatment	7
E. G. H.	F	15	Cough 5 mo., chills and fever	Atelectasis of right lower lobe	Forceps, electrocoagulation, x-ray	Symptoms minimal	15
A. J.	F	39	Prod. cough 2 yr., attacks of "pleurisy" and "pneumonia"	Atelectasis of right lower lobe	Forceps	Symptoms minimal	2
A. L.	F	33	Prod. cough 2 yr., "pneumonia," T.b. sanatorium 9 mo.	Atelectasis of left upper lobe	Forceps	Symptomatic improvement	8
M. L.	F	33	Cough 4 yr., wheezing, "pneumonia"	Atelectasis of right lung	Forceps, electrocoagulation	Symptomatic cure	4½
E. M.	F	45	Prod. cough 5 yr., hemoptysis, occasional pain	Atelectasis of left lower lobe	Forceps, radon seeds, x-ray	Symptomatic cure	15
A. R.	F	32	Hemoptysis 2 yr., attacks of "Influenza" and "pleurisy"	Atelectasis of left lower lobe	Forceps	Symptomatic cure	14
B. G.	F	44	Prod. cough 4 mo., wheezing 4 yr., hemoptysis	Atelectasis of left lower lobe	Forceps, electrocoagulation	Improved, still under treatment	4
S. S.	F	38	Cough 3 yr., hemoptysis 3 yr.	Atelectasis of left lower lobe	Forceps, x-ray	Symptomatic improvement	23
M. S.	F	37	Cough 5 yr., hemoptysis, "pneumonia"	Atelectasis of left lower lobe	Pneumonectomy 11/19/40	Death 4 days postoperative	5
E. T.	F	25	Hemoptysis 10 yr., cough, "pneumonia"	Atelectasis of right lower lobe	Forceps, electrocoagulation	Improved, still under treatment	23
L. W.	F	19	Hemoptysis 6 mo., cough	Atelectasis of right lung	Pneumonectomy 6/2/39	Cure	5½

capillary. When these latter are seen in cross section they resemble the pseudo-rosette seen in tumors of the nervous system. Although in all these respects the picture varies, one is impressed by the constancy of size and shape of nuclei except where regression has occurred.

The characteristics of the stroma are: (1) It is often dense and poor in cells where regression is occurring. (2) Frequently it is rich in capillaries and there is interstitial hemorrhage; proliferating fibroblasts invade the clot and surround the tumor cell masses. It may be this fibrous growth which brings about regression, for the denser areas often contain hemosiderin-like deposits. (3) Where hemorrhage has not occurred, the capillaries wind in and out around the acinus-like

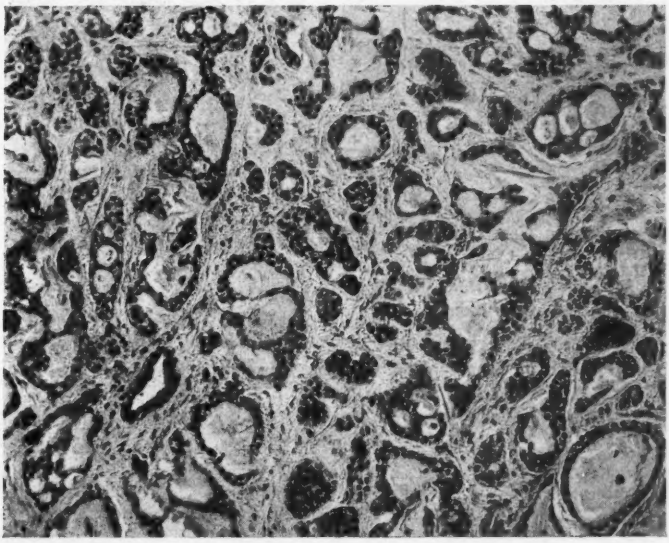


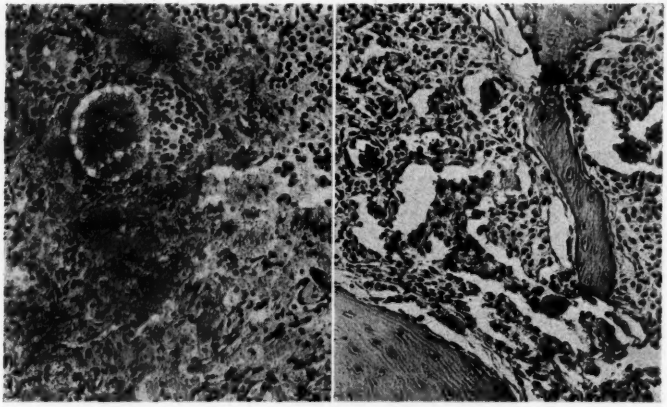
Fig. 2.—We originally called this tumor a bronchial adenoma, believing that the degree of maturity of cells as evidenced by the more or less faithful reproduction of glands indicated benign character. Further studies of this and other cases brought us to the realization that the histologic pattern is not at all like that of the tumors we consider to be bronchial adenomas today.

structures, and as Womack and Graham[4] have pointed out, the pictures may closely resemble fetal lung. The first time I was confronted with an adenoma of this type I called it "herniated atelectatic lung tissue." These observations suggest to me that these cells are attempting, in adult life, to do what they were destined to do in embryonic life, namely, to form pulmonary alveoli.

Rarely, the active growth of epithelium with the polyhedral cellular outline surrounded by rapidly proliferating capillary endothelium (and among these latter cells mitoses may appear) produces a disturbing picture which may easily lead one to an erroneous diagnosis. I have not seen proliferating muscle cells in the tumors I have studied.

I have encountered cartilage and bone in one (Fig. 3). In this case both were typically adult and not at all like the neoplastic cartilage seen in chondromas or mixed tumors of the salivary glands. These tissues seem to be incidental to, but not part of, the tumor.

I believe bronchial adenomas may infiltrate the wall of the bronchus and any tissue that comes in their path, just as a basal-cell carcinoma



A. *B.*

Fig. 3.—*A*, The upper third shows the rather characteristic cellular growth. The lower two-thirds show the peculiar connective tissue reaction. The dark area below the larger cell mass is the seat of hemosiderin deposit. Surrounding this, note the vascular proliferation.

B, This photograph shows the characteristic neoplastic cellular growth. Here also there is seen some typical bone formation, not a frequent occurrence in our cases.

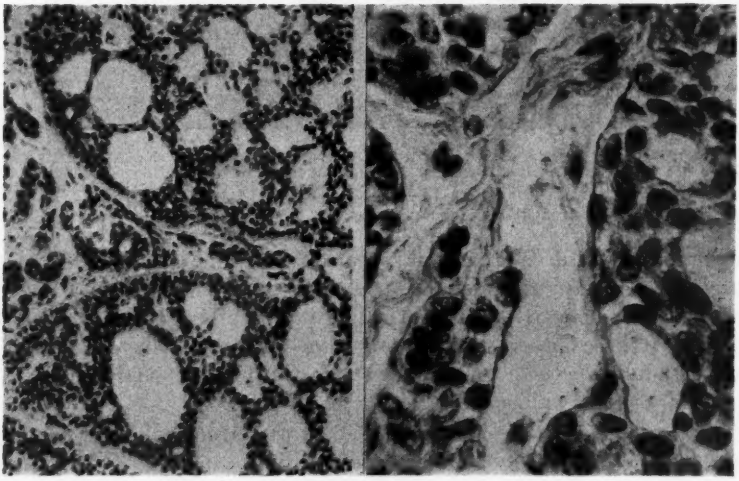


Fig. 4.—In some respects the arrangement of cells is like that of benign adenoma, but note the pleomorphism which to us is inconsistent with the histologic picture of benign adenoma. Distinct lumina do not occur in the cell masses of bronchial adenoma, and there is little or no evidence of secretory activity. (This is another case in which our own original diagnosis was incorrect.)

of the skin might do. However, I believe such infiltration is sufficiently infrequent, and limited when it does occur, that endobronchial removal is justified where it can be done, admitting that complete removal by this means is often not possible, and that, obviously, incompletely removed tumors will recur. Furthermore, repeated removal does not seem to cause more rapid growth or to alter the behavior of the remaining cells as it does in basal-cell carcinoma of the skin. I have seen no evidence of metastasis by blood or lymph stream. That these tumors *may* undergo malignant change must be admitted, although I have not encountered such a change, nor have I seen a malignant tumor which I believe started as a benign adenoma. Such malignant change would be evidenced by pleomorphism and variation in size of nuclei, with distinct alteration in chromatin markings and with active mitosis. The experience of the Jackson Clinic would indicate that malignant change is uncommon. It is true that the picture in different portions of the same tumor may vary, and diagnostic accuracy demands that the histopathologist see the whole picture. It is our custom to section the whole tumor if it is small, or numerous fragments if it is large. Serial sections are prepared for microscopic study from several layers of each nodule or fragment.

TREATMENT

Obviously, discussion of the therapeutic indications presupposes that a definite diagnosis of bronchial adenoma has been established, and this must mean that at least one bronchoscopy has been done and that tissue has been removed bronchoscopically for biopsy. While the clinical picture may be very suggestive of bronchial adenoma, the diagnosis cannot be proved without biopsy, and bronchoscopy affords the only means of doing this. These tumors do not lend themselves to needle biopsy, and let us hope that lobectomy or pneumonectomy has not been done to establish the diagnosis, regardless of what we may conceive to be indications for lung resection in treatment! It is well known that only about 75 per cent of the cases of carcinoma can be biopsied bronchoscopically, but this figure does not apply at all to adenomas, because they characteristically occur in the portions of the bronchial tree accessible to bronchoscopic inspection.

Bronchoscopic Treatment.—Let us assume that some of the tumor has already been removed for biopsy. We believe that several additional bronchoscopies should be done in all cases for the relief of bronchial obstruction. This can be accomplished by piecemeal forceps removal, by electrocoagulation, or by a combination of the two. Electrocoagulation has the advantage of much less bleeding, and it is therefore safer and more efficient in most cases, but we have often found it advantageous to alternate forceps removal with electrocoagulation.

In the cases where it is found possible to remove the tumor bronchoscopically, and thus bring about drainage and reaeration of the distal

portion of the bronchial tree and lung, there is no harm in postponing more radical treatment. On the other hand, such patients should be kept under observation and re-examined at intervals, because as has already been implied, these tumors unquestionably do tend to recur, or perhaps it might be more accurate to say that their complete removal by bronchoscopic means is difficult and in many instances impossible. Our point is, that if we succeed in accomplishing drainage and reaeration, there is not any *urgent* need for the use of more radical measures. In some cases, the bronchus will remain open without any further treatment; in others with only very occasional subsequent treatments.

Indications for Lung Resection.—As we see it, lobectomy or pneumonectomy is indicated: (1) in cases of bronchial adenoma in which, because of sessile attachment and size, bronchoscopic removal is not feasible; and (2) in cases where cavitation, bronchiectasis, or other severe damage to the distal portion of the lung has resulted from prolonged bronchial obstruction. We should like to emphasize the fact at this point, however, that a very different situation obtains in the case of bronchial adenoma than in the case of carcinoma, in so far as urgency is concerned, provided drainage and aeration can be re-established. These tumors are slow growing, they do not metastasize, and *they do not have any inherent tendency to become malignant,* if they ever do so. The contrary impression, in our opinion, has been due to confusion and error in histopathologic diagnosis.

RESULTS IN OUR SERIES OF 20 PATIENTS

The clinical course and present status of our twenty cases are shown in Table I. Three of the patients in the series were treated by lobectomy or pneumonectomy, two by Dr. W. E. Burnett and one by Dr. Richard Meade. The others have all been treated by bronchoscopic measures only, though lung resection has been advised in several instances.

SUMMARY AND CONCLUSIONS

1. The clinical features of twenty cases of so-called adenoma of the bronchus are shown in tabular form.

2. An attempt is made to standardize the histopathologic diagnosis of this type of tumor.

3. The differential pathologic diagnosis between adenoma and low-grade adenocarcinoma, and some other tumors, is considered.

4. We do not believe that adenomas have *any inherent tendency* to metastasize or in any other way "become malignant." None of our patients has shown such a course, though a number have been under observation for ten years or longer.

5. The possibility of extrabronchial growth of adenomas, producing a "collar button" lesion with the larger part outside the bronchus, is recognized but thought to have been overemphasized by many.

6. Bronchoscopic treatment by forceps removal, electrocoagulation, and aspiration is indicated as the first step in all cases; it will be curative in some, palliative in others. In cases where there is atelectasis or bronchiectasis, a preoperative course of bronchoscopic treatment is indicated, even if lung resection has been definitely decided upon or is to be considered at a later date.

7. Lobectomy or pneumonectomy is indicated when bronchoscopic cure of the bronchial lesion seems impossible, or when prolonged bronchial obstruction has resulted in serious permanent damage to the distal portion of the lung.

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(See discussion on page 119.)

THE PROBLEM OF THE SO-CALLED BRONCHIAL ADENOMA

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(BY INVITATION)

ST. LOUIS, MO.

THE so-called bronchial adenoma is now known to be a common tumor, although until the last ten or fifteen years it was regarded as rare. This tumor has certain well-recognized characteristics. It nearly always occurs in a primary bronchus or close enough to one to permit visualization by the bronchoscope. Atelectasis of a lobe or of the whole lung therefore is common, and bronchiectasis in association with the obstruction is frequent. Women are slightly more often affected than men, a feature which is in marked contrast to the overwhelming preponderance of ordinary carcinoma in men. In general, the symptoms produced by the tumor appear at an earlier age than those caused by ordinary carcinoma and may even be present in childhood and adolescence. The bronchoscopic appearance is usually typical. A smooth rounded mass, often pink because of its vascularity, is seen projecting into the lumen of the bronchus. Its attachment is generally by a broad base. In fact it often happens that only a small portion of the tumor is endobronchial and that most of it is outside the bronchus. In this respect these tumors may be likened somewhat to an iceberg which has only a small portion visible above the surface of the water. Ulceration of the tumor is rarely seen, although hemoptysis is a fairly frequent complication. It is commonly associated with other abnormalities of the lung, for example, either absence of interlobar fissures or excessive lobulation, congenital cystic disease, or abnormal bronchi.

The microscopic appearance conforms fairly well to a rather definite pattern. The tumor itself is covered by bronchial epithelium which often has undergone squamous metaplasia. Directly beneath this layer there is usually fibrous tissue which varies so much in thickness that, although in some cases it is extremely thin or practically absent, in others it is so thick that it may be difficult to obtain a biopsy of the real tumor tissue. Sometimes this fibrous tissue is edematous. The main portion of the tumor is composed of cells with scanty cytoplasm and small, round, darkly staining nuclei in which mitotic division is rarely seen. These cells are often arranged in such a manner that the resemblance to fetal pulmonary alveoli is very striking. These alveoli are separated by a stroma which consists chiefly of blood vessels and loose edematous fibrous tissue. In some cases the cells are arranged in cords giving the impression of a hypernephroma. It is our opinion that

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in many cases diagnosed as metastatic hypernephroma of the lung the true condition is a so-called bronchial adenoma. Sometimes the stroma is so vascular that an impression of an angioma may be gained. The diagnosis of endothelioma has often been made in such cases. In some tumors the stroma has been dominated by cells of mesoblastic origin with the result that areas of fibrosis, smooth muscle, fat, fibrous and hyaline cartilage, and even bone have been seen. An important feature of these tumors is that in many of them sections taken from different portions reveal very different appearances. In places there is a small amount of stroma and the epithelial cells are larger, giving an impression of more malignant growth. In some areas a glandular arrangement may be suggested and a diagnosis of adenocarcinoma made. Again the alveolar arrangement of the epithelium may give rise to the term "alveolar carcinoma." In parts of the tumor there are sometimes found strands of smooth muscle and occasionally nests of fat cells.

The resemblance to fetal lung which some of these tumors exhibit is often so striking that it would be extremely difficult, if not impossible, to distinguish one from the other on the basis of microscopic sections. This close resemblance probably furnishes a clew to the origin of these tumors in that it suggests that they are derived from disorganized embryonic bronchial buds which have failed either to pursue a normal development or to have atrophied. The position of these tumors in the walls of the larger bronchi is also suggestive of such an origin.

The fact that the so-called bronchial adenomas have some characteristics like those observed in certain tumors of the salivary glands which are commonly called "mixed tumors" led us, in 1938,[1] to designate them as "mixed tumors of the lung." These characteristics are the presence of cartilage and sometimes even bone, the tendency to invade neighboring tissues directly when they have shown malignant tendencies, and, in our opinion, the occasional exhibition of tumor formation by the connective tissue elements. This last characteristic might be questioned by many pathologists. It is our belief, however, that in many cases of chondroma, fibroma, lipoma, myxoma, and even sarcoma of various types found in the lung the origin of the tumor has been the same as that of the so-called adenoma or "mixed tumor" of the bronchus but in which the connective tissue or mesodermal elements have proliferated without a corresponding proliferation of the epithelial tissue. Albrecht[2] in 1904, coined the term "hamartoma" in connection with a tumor of the liver by which he meant to express the opinion that it was the result of an abnormal growth of the normal structures of the organ.

In accordance with a line of reasoning similar to Albrecht's conception of "hamartoma," we have felt that many of the tumors of the lung result from the failure of embryonic bronchial buds to develop into normal structures, and in our 1938 article[1] we called attention to the similarity of our own conception of the origin of these tumors to that of Albrecht for the tumor of the liver described by him. These buds consist of

both entoderm and mesoderm. It would seem reasonable, therefore, to consider that tumors might appear in adult life which had their origins in either embryonic entoderm or mesoderm. In accordance with our ideas, two main groups of pulmonary tumors can be thought of as occurring from a failure of a bronchial bud to develop into a normal adult arrangement of tissues. These two groups are (1) those in which the mesodermal elements predominate and (2) those in which the entodermal (or epithelial) elements are dominant. The former group, then, would include such tumors as those which are usually designated as chondroma, osteoma, fibroma, lipoma, angioma, myxoma, and sarcoma. The second group is illustrated chiefly by the so-called adenoma. This would explain the extreme frequency of the occurrence of epithelial elements in so-called chondroma of the lung and mesodermal elements in the epithelial tumors.

The chief clinical problem which these tumors present concerns the question of whether or not they are to be regarded as either actually or potentially invasive in nature or whether they should be considered purely benign in type. It is difficult to understand how there could be any controversy on the point at this time. If one accepts as criteria of malignancy, invasion of adjacent tissues, involvement of regional lymph glands, and metastasis to distant organs, then in the light of a considerable amount of published experience one cannot deny that there have been authentic examples of these tumors becoming malignant. For now there have been many cases recorded in which the three criteria of malignancy mentioned have been present.

In 1938, we[1] advanced the opinion that the so-called bronchial adenoma is potentially malignant and we reported seven cases out of a larger group in which either invasion of adjacent tissues or involvement of regional lymph glands had occurred. Kirch,[3] von Pein,[4] and Malkwitz[5] had previously reported cases of malignant transformations of "adenoma" or "polyp," but little or no attention was paid to their reports. Moreover, it is not certain that in all the cases the authors were presenting the same sort of tumor as that under discussion here. The opinion which we expressed in 1938 was not then generally accepted, and by many it is still regarded with skepticism. In 1942, however, Adams, Steiner, and Bloch[6] reported five cases under the designation of "malignant adenoma of the lung." In one of their patients there was a metastasis to the vertebral bone marrow; one had metastases to both the mediastinal lymph glands and to the liver; in another there was involvement of a tracheobronchial lymph gland; and in two the bronchial wall itself was invaded. Anderson,[7] of the Department of Pathology of Washington University, has recently reported a case in which there was a metastasis in the liver. Stowell,[8] also of the Department of Pathology, in an unpublished case of an autopsy at the St. Louis County Hospital, has found a metastasis in a regional lymph gland.

It would appear, therefore, that there is plenty of incontrovertible evidence that at least some of these tumors have fulfilled all the requirements of malignancy.

Again there is the case reported by Burrell[9] which seems to us to be so important that we quote at length from his report.

> Mr. Negus has referred this evening to a case which he (the speaker) had seen some years ago. The patient was a young woman who had hemoptysis; she was in a sanatorium for fourteen months, but no evidence of tuberculosis could be found. After the fourteen months in a sanatorium, lipiodol was put into the trachea and x-ray examination showed a blocked bronchus. Mr. Negus, on bronchoscopic examination, discovered a fibro-adenoma which was the cause of the hemorrhage. He removed it, but several years after the operation carcinoma of the bronchus developed and the patient died. Even the polypoid and apparently innocent growth might contain some malignant cells.

Of course, Mr. Negus did not remove all of the "fibro-adenoma." Probably in the majority of cases it is impossible to remove all of such tumors through the bronchoscope.

We have had a case, previously unreported, very similar to, and of equal importance to, the case of Burrell and Negus just mentioned. In our opinion this presents incontrovertible evidence that the so-called bronchial adenoma may become malignant and cause death. The case report follows:

H. C. K. (No. 15806), a physician, entered Barnes Hospital, June 7, 1928, stating that he had had a bad cough and had been subject to "colds" for twenty years. For the past six weeks he had had fever and bloodstreaked sputum. On June 11, 1928, Dr. Arbuckle on bronchoscopy found so much blood coming from the right lower lobe bronchus that further examination was postponed. On June 18, he found in the lower portion of the right main bronchus a mass which moved in and out with respiration. It was of the size and shape of an almond kernel and practically filled the lumen of the bronchus. It bled freely when cut into for biopsy.

Microscopic examination of the biopsy material showed the characteristic appearance of the so-called bronchial adenoma. The cells had scanty cytoplasm and small, round, darkly stained nuclei. No mitotic figures were seen. The cells were not arranged in any definite order. No evidence of cartilage or bone was noted. Since the material was obtained by bronchoscopic biopsy it was only a small fragment. Possibly a larger portion would have shown other features not noted in the examination of this material. Figs. 1 and 2 are photomicrographs of the biopsy specimen.

July 20, 1928, Dr. Arbuckle performed an extensive cauterization of the mass through the bronchoscope by means of the galvanocautery. This was repeated Aug. 3, 1928, and on re-examination Dr. Arbuckle felt satisfied that he had destroyed the mass successfully.

The patient was readmitted to the hospital, Oct. 3, 1929, fourteen months later. He stated that during the preceding winter he had felt well except that he had had a "few mild attacks of coughing with occasional hemoptysis." He had gained weight and was able to practice medicine. In March, 1929, he developed "pneumonia" suddenly in the right lower lobe. After eight weeks he felt well again and continued

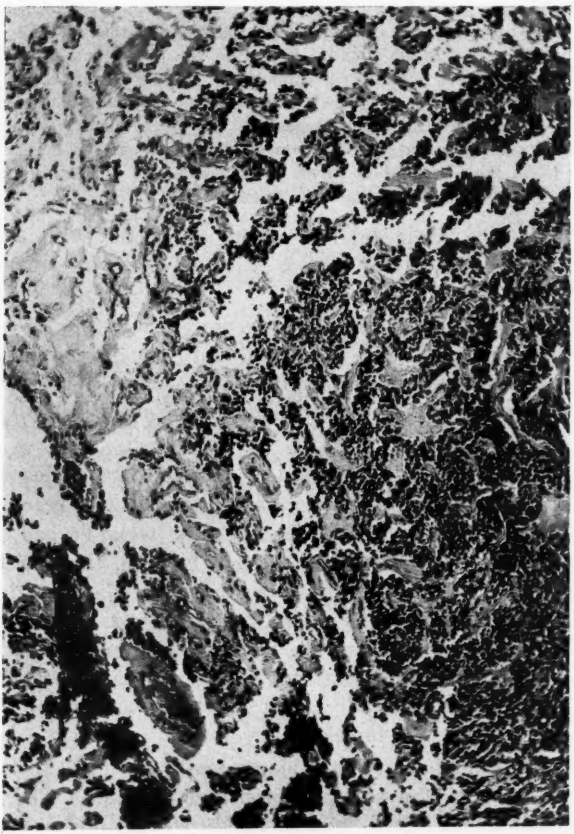

Fig. 1.—H. C. K. Section made from bronchoscopic biopsy in 1928 showing common features of mixed tumor or so-called adenoma of bronchus. No orderly arrangement of cells; large nuclei and scant cytoplasm. This characteristic is seen better in Fig. 2.

free of symptoms during the summer. A month before admission to the hospital he had a return of cough, fever, and bloodstreaked sputum, which had persisted. The patient declined to have a bronchoscopic examination at this time, although it was understood that he would return in three weeks for that purpose. He failed to return.

Three years later, in response to an attempt at a follow-up, a letter was received Dec. 30, 1932, from Dr. Wm. H. Field of Evansville,

Indiana, stating, "Dr. K. died on Sept. 10, 1932. Post-mortem examination showed a large mass of cancerous tissue in liver and lung." Unfortunately it was not possible for us to obtain any of the tissue for microscopic examination since none of it was saved.

This case then is another example of a so-called adenoma which undoubtedly pursued a benign course for more than twenty years before becoming malignant. Like the case of Burrell and Negus it seemed at

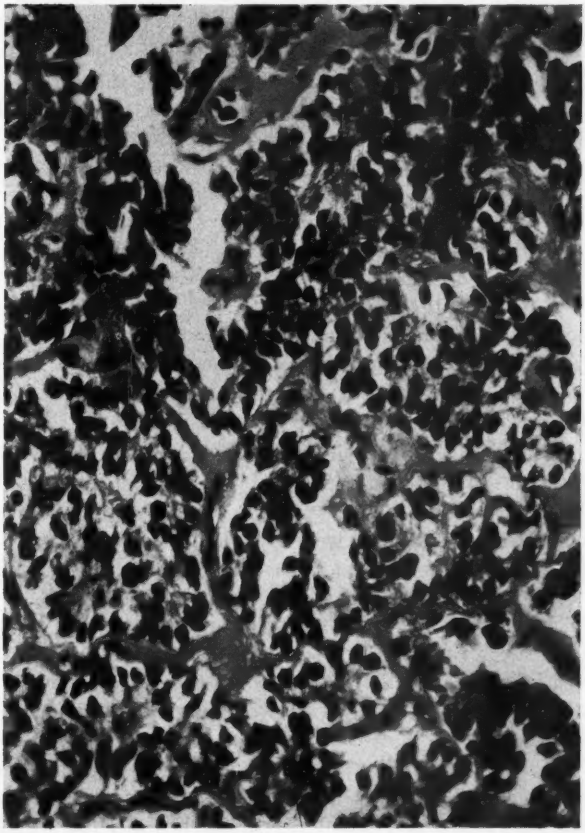

Fig. 2.—H. C. K. High-power magnification of bronchoscopic biopsy, four years before death of the patient from carcinoma of lung and liver. The typical cells of mixed tumor or adenoma are seen, characterized by large nuclei with scant cytoplasm. No mitotic figures are seen. The cells are arranged in a manner loosely suggestive of an adenoid structure.

one time that the tumor had been completely removed through the bronchoscope. Yet enough was left to develop an extensive carcinoma with a metastasis in the liver.

Two other cases of ours may be cited as presenting evidence of a malignant transformation of these tumors.

H. J. P. (No. 83732), aged 42 years, a druggist, was admitted to the Barnes Hospital Aug. 2, 1940. His symptoms were very unusual in that his only complaints were weakness in his legs for about four weeks and easy fatigableness. He had no appreciable cough, no hemoptysis, and no chest pain.

Bronchoscopy by Dr. Blades, August 8, showed the bronchus of the left lower lobe blocked by a tumor. The diagnosis of the biopsy material was a mixed tumor of chiefly epithelial elements. August 14, a total left pneumonectomy was performed with difficulty because the bronchial lymph glands and other hilar structures were apparently involved.

The surgical pathologic examination (No. 35938) showed the bronchus of the left upper lobe to be almost completely plugged with tumor tissue. Several lymph nodes near the hilus were apparently invaded by the tumor. The upper lobe was atelectatic. The borders of the tumor were irregular. The microscopic examination revealed the tumor to consist of epithelial cells surrounded by a mucoid type of active connective tissue. The cells, however, in certain regions were seen to grow in large sheets and clumps loosely invested in dense connective tissue stroma. The cells themselves consisted of epithelial elements with moderate-sized nuclei and practically no cytoplasm. The nuclei had a reticular type of arrangement of chromatin and there were many mitotic figures. The tumor was extremely invasive. Some of the lymph nodes were almost entirely replaced by tumor cells.

The patient died Aug. 16, 1940. At autopsy (No. 8805) there was found metastatic carcinoma of the left tracheobronchial lymph nodes and of the liver. Scattered through the parenchyma of the liver, most numerous beneath the capsule, were over thirty light yellow, well-defined, soft, spherical nodules varying from a few mm. to 1 cm. in diameter. The microscopic examination revealed sections of two left tracheobronchial lymph nodes showing scant remains of lymphoid tissue. Most of the nodes were replaced by large irregular masses, cords, and strands of neoplastic epithelial cells which were irregularly oval, moderate-sized cells with scant cytoplasm and with oval, hyperchromatic nuclei. There were several atypical mitotic figures. The peripheral cells of the masses tended to have a radial arrangement and the central portions had no definite pattern. There was a small amount of fibrous stroma. The section of liver showed a nodule of tumor beneath the capsule. The tumor was slightly more cellular but was similar to that described in the lymph nodes.

This case seems certainly to be an example of a so-called adenoma which has become malignant with metastases not only to the regional lymph glands but also to the liver. The gross appearance of the tumor and its microscopic structure seem clearly to place it in that group. One may conjecture also that if it had been seen earlier, before metastases had occurred, it would have been considered by many as a benign tumor or so-called adenoma of the bronchus. (See Figs. 3 and 4.)

The second of these two cases was encountered after this paper was presented at a meeting of the American Association for Thoracic Surgery. It is added, however, because of its special interest in connection with the thesis developed in the article.

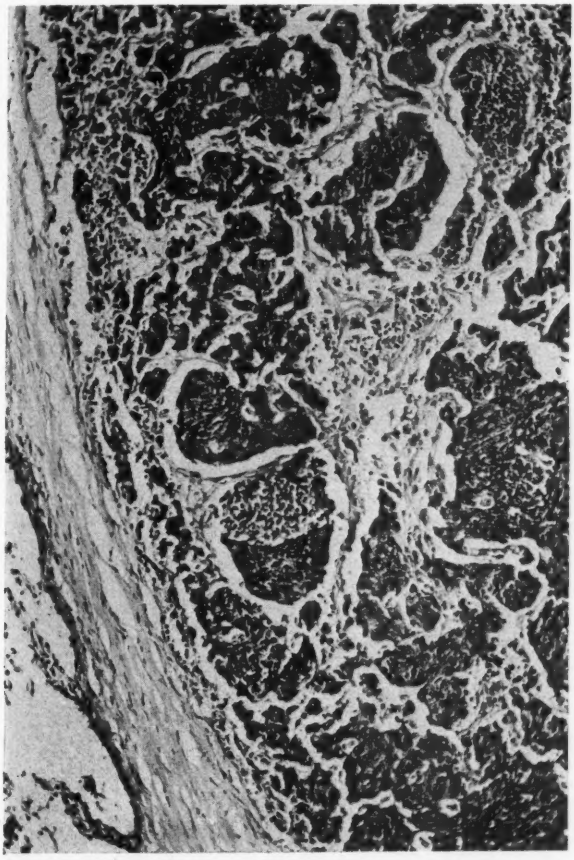

Fig. 3.—H. J. P. Section of bronchial tumor showing characteristic morphology of mixed tumor or adenoma. The cells are chiefly epithelial and are characterized by moderate-sized nuclei with practically no cytoplasm. They are not arranged in any definite order.

N. V. (No. 119382), a white porter, aged 51 years, was admitted to Barnes Hospital Nov. 8, 1944. He had had a cough for several years but it had been severe for only about one year. During the last few months there had been very severe paroxysms of coughing but with very little sputum. There was no hemoptysis. He had pain in the right chest and a loss of fourteen pounds during the last year. X-ray examination showed an area of infiltration over the right upper lung

field and an obstruction of the right upper lobe bronchus. Bronchoscopy on November 9 revealed a papillary tumor protruding from the right upper lobe bronchus.

A right total pneumonectomy was performed on November 15. The patient made an excellent recovery.

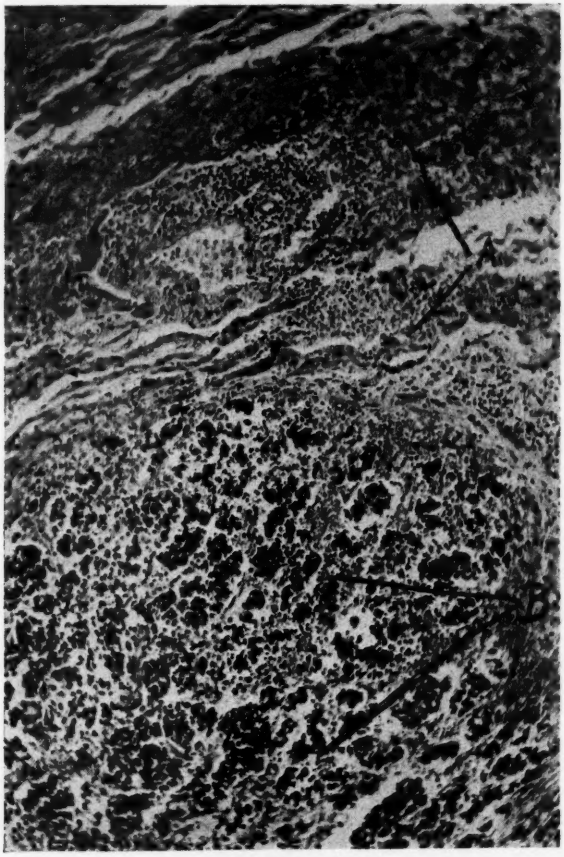

Fig. 4.—H. J. P. Metastasis in liver. At *A* is seen liver tissue and at *B*, the metastasis in which the characteristic features of so-called adenoma or mixed tumor are seen. Mitotic figures are atypical and very infrequent.

Gross pathologic examination revealed no evidence of tumor in adjacent lymph nodes. The bronchus to the upper lobe was obstructed approximately 1 cm. above its external opening and a small mass of tumor could be seen protruding into the lumen. On cut section the upper lobe was seen to be involved by a tumor which extended almost to the visceral pleura, ending about 2 cm. above the lobar fissure. This mass was irregularly oval near the bronchial orifice but on approaching

the apex the tumor was seen to separate into three smaller oval parts. The tumor was very firm, white throughout, and seen to be surrounded by a capsule 1 mm. in diameter. The tumor completely obstructed the upper lobe bronchus but did not reach the surface of the lung. Bronchioles of both upper and lower lobes showed some bronchiectasis and pus was expressed from the upper lobe. No gross cysts were seen.

On microscopic examination sections showed an extremely bizarre malignant tumor of the lung in which both epithelial and connective tissue elements were taking part. Elongated cords and islands of malignant epithelial cells could be seen growing within a fibrous tissue stroma. The epithelial cells were extremely anaplastic, rapidly growing with numerous mitotic figures. The individual cells were variable in size, shape, and staining reaction. In many areas central degeneration could be seen with debris resembling keratin within the degenerated areas. The stroma was the most remarkable part of the tumor. It was extremely cellular, the individual cells were spindle shaped, and the nuclei showed evidence of rapid growth with numerous mitotic figures. With the Masson stain these cells could be seen to be actively laying down collagen and were definitely fibroplastic in origin. In other areas the sarcomatous appearance was less marked and malignant epithelial cells were growing in an inactive stroma. Bone formation was evident in places. In some areas the tumor had the appearance of arising from the wall of a cyst in which the wall had actively taken part in the malignant change. The lung parenchyma distal to the tumor showed some bronchiectasis and chronic inflammatory change with areas of atelectasis surrounding the bronchi. Diagnosis: Mixed bronchiogenic carcinoma and sarcoma.

This case seems to us to be an outstanding example of a malignant transformation of a tumor which, if seen earlier, would have been designated by many as a bronchial adenoma. But more interesting and more important than that is the fact that both the epithelial and connective tissue elements have become malignant. This is in line with our previous ideas that theoretically either the entodermal or mesodermal elements of a latent bronchial bud may take on the features of a neoplasm and that either type of element may become malignant. Further support of our use of the term "mixed tumor" of the bronchus is lent by the presence of bone in this particular tumor which is both a carcinoma and a sarcoma. (See Figs. 5 and 6.)

There is no doubt that many of these tumors when first seen are benign, that is they may not demonstrate the presence of any of the commonly recognized criteria of malignancy. It is probable also that some patients with these tumors fulfill their normal life span before the tumors become malignant. Certainly there is abundant evidence that sometimes the patient has had symptoms from such a tumor for many years, twenty years or so. Yet it is a striking fact that it is rare to find a bronchial adenoma at autopsy, especially after middle age.

There are apparently many more found during life at the present time by bronchoscopy, and there are certainly many more cases diagnosed as bronchiogenic carcinoma found at autopsy. We believe that the explanation of this discrepancy lies in the fact that the majority of these tumors become malignant and that after they have developed full-blown features

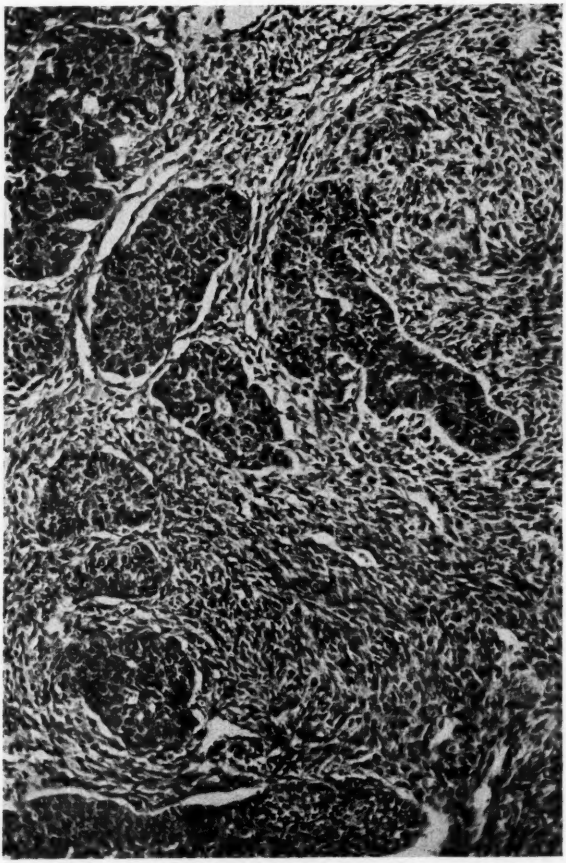

Fig. 5.—N. V. Combined carcinoma and sarcoma. Section of tumor in lung showing wild disorderly and very malignant fibroplastic tissue. The epithelial cells in groups surrounded by the sarcomatous tissue also show definite evidence of malignancy. They are anaplastic, and mitotic figures are numerous.

of malignancy the identity of the original tumor is lost. In this respect an adenoma of the bronchus would be merely following the rule of what is well established in regard to adenomas of other organs, for example, the breast, the prostate, the thyroid, the rectum.

If we should imagine a malignant change occurring in a so-called bronchial adenoma, we should expect that the prevailing type of epithelial cell would be one that is small, round, with scanty cytoplasm

and darkly staining nucleus, in other words the type of epithelial cell found in the adenoma. This corresponds very well with the predominating type of cell which is found in two very common kinds of carcinoma, designated according to orthodox pathologic standards as "oat-cell carcinoma" and "round-cell carcinoma." Again, the areas in an adenoma which look like fetal lung bear some resemblance to an adenocarcinoma.

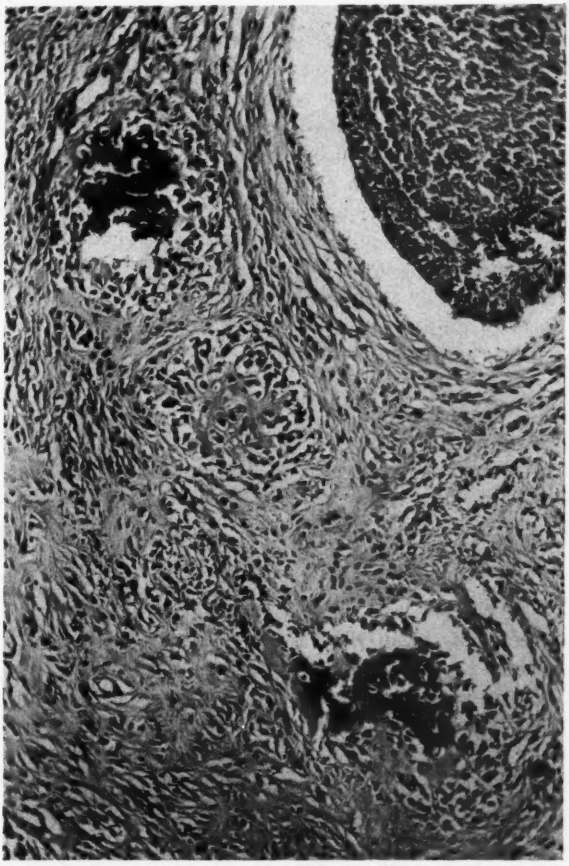

Fig. 6.—N. V. A section made through another part of the tumor showing two areas of bone formation.

In view of the well-established malignant potentialities of the so-called bronchial adenoma the principles of treatment become clear. It seems to us that radical surgical removal becomes a procedure of choice. Because of the frequency with which one finds a large portion of the tumor outside the bronchus it would appear that only rarely could it be completely removed through the bronchoscope. In many instances the

attempt to remove it in this manner will be particularly hazardous because of the danger of perforation of the bronchus. If it is not completely removed there will always be the danger of a later invasion by the part left behind, as in the case cited by Burrell and the one of ours described here. An additional objection to the local removal of the tumor is the uncertainty in many cases whether or not it is actually malignant at the time of operation and, if so, the extent of its spread. The piece of tissue which has been removed by bronchoscope for biopsy may not show clear evidence of malignancy even when the tumor has already invaded neighboring tissues or regional lymph glands. Still another reason why bronchoscopic removal is likely to be unsatisfactory is that often there is an associated bronchiectasis due supposedly to the bronchial obstruction produced by the tumor. Lobectomy undoubtedly will sometimes prove to be an adequate operation, but it is our opinion that often it will not be adequate because of the location of the tumor. We prefer, therefore, the operation of total pneumonectomy for these cases. The removal of possibly involved regional lymph glands can be much more satisfactorily accomplished in that way. In good-risk patients there is scarcely, if any, greater danger from the operation of total pneumonectomy than from lobectomy.

SUMMARY

The so-called bronchial adenoma must be regarded as a potentially malignant tumor. Although it may pursue a nonmalignant course for many years there always remains the possibility of the appearance of malignant qualities, such as invasion of neighboring structures, involvement of regional lymph glands, and the development of distant metastases.

Evidence of the potential malignancy of these tumors, in addition to that presented by us in 1938, is given here. Also a case is cited in which there was a combined carcinoma and sarcoma with the presence of bone. The malignant transformation of both the epithelial and connective tissue elements in this case seems to us to support our suggestion made in 1938 that a wide variety of tumors can be thought of as arising from a fetal bronchial bud which has failed either to develop normally or to atrophy. At that time we offered the conception that either the mesodermal or entodermal elements could be the origin of later neoplastic growth which could include not only such recognized pulmonary tumors as chondroma, fibroma, lipoma, sarcoma, etc., but also the so-called adenoma which is composed predominantly of entodermal or epithelial elements. It is rare, however, to find malignant transformation of both elements in the same tumor. The presence of bone in this case we feel also is in line with our conception that "mixed tumor" is a better designation of these tumors than "adenoma."

The frequent inability to determine from a biopsy specimen whether or not at the time the tumor has already become malignant makes the

attempts at local removal through the bronchoscope both unwise and dangerous. Total pneumonectomy is the procedure of choice.

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DISCUSSION ON "DIFFICULTIES IN THE DIFFERENTIAL DIAGNOSIS OF BRONCHOGENIC CARCINOMA" BY DR. ROBERT G. BLOCH, DR. WILLIAM E. ADAMS, DR. THOMAS F. THORNTON, AND DR. J. EDMOND BRYANT*; "BRONCHIAL ADENOMA" BY DR. CHEVALIER L. JACKSON, DR. FRANK W. KONZELMANN, AND DR. CHARLES M. NORRIS†; "BRONCHOSCOPIC CINEMATOGRAPHY OF BRONCHIAL TUMORS" BY DR. PAUL HOLINGER‡; AND "THE PROBLEM OF SO-CALLED ADENOMA OF THE BRONCHUS" BY DR. EVARTS A. GRAHAM AND DR. NATHAN A. WOMACK

DR. RALPH ADAMS, Boston, Mass.—Mr. Chairman: I am the young man who regaled Dr. Brown with case histories on his visit to Dr. Churchill's clinic. During my eight years of training under Dr. Churchill and Dr. Sweet it was my task to review all the lung tumors, including 1 sarcoma, 155 carcinomas, 1 hamartoma, 1 neurofibroma, and 17 bronchial adenomas. Purely on the basis of pathologic examination the diagnosis was made, but the clinical history, operative findings, and subsequent course so closely paralleled it that we thought the parallelism was more than coincidence.

Of the 175 cases, 17, or 10 per cent of all the lung tumors, were bronchial adenomas; in 5 there was bronchoscopic removal. One was an incidental autopsy finding, and the remaining 11 were resected because of peripheral lung destruction.

Fifteen of the 17 patients with adenoma, or 88 per cent, are living and well from three to five years later. To be compared with these are 5 of the 155 patients with carcinoma, or 3 per cent, living for the same period. Stated differently, of 28 patients with surgically resected malignant tumors, 3, or 11 per cent, have a chance of five years' survival. Of 11 patients with surgically resected adenomas, 10, or 90.9 per cent, are living and well, and none has as yet shown signs of malignant degeneration. Some of these cases showed local glandular involvement.

In other words, we have not yet had evidence in this group of cases to support the theory that bronchial adenoma is a malignant tumor. Secondly, we would plead for a clear statement of what is being included in the statistical reports of resection in carcinoma of the lung. For example, if all of the 39 cases of resected tumors in the series are called carcinoma, thirteen of the patients are living and well, making a survival rate of 33 per cent instead of 3 per cent, which is the true situation.

*See page 83 for article by Bloch, Adams, Thornton, and Bryant.

†See page 98 for article by Jackson, Konzelmann, and Norris.

‡The presentation by Holinger mentioned in the discussion was a moving picture demonstration. No paper on the subject was included.—Editor.

DR. HERBERT C. MAIER, New York, N. Y.—As Dr. Graham has mentioned, there is considerable variability in the histopathology of so-called adenomas of the bronchus. The case that he referred to as being reported by Dr. Anderson from his clinic shows one of these variations. In that case the glandular formation is somewhat more striking than in most other cases of bronchial adenoma. I have seen two cases of a similar type, and in reviewing the so-called adenomas that have been reported in the literature, Dr. Johnson and I were able to separate twenty-five to thirty cases that seemed to be of this special variety. An interesting observation in this subgroup has been that more than 50 per cent of these tumors have been either close to the carina, projecting into the trachea from the bronchus, or arising in the tracheal wall. Also, there has been a somewhat higher incidence of malignant characteristics than among other adenomas. Due to the location of the tumors in this particular subgroup, the mortality rate has been much higher than in ordinary bronchial adenomas because a number of patients have died from tracheal obstruction.

DR. J. J. SINGER, Los Angeles, Calif.—In discussing Dr. Bloch's paper, I believe that those of us whose job it is to work up the cases will find just such difficulties as he shows. The x-ray evidences of masses, especially the small ones, show them to be the ones that are best suited for surgery if they are malignant, but they are the ones that give us the greatest trouble in the proper diagnosis.

We often see the small ones that disappear and sometimes they remain for years without any change. We also know that some of them are the so-called calcified abscesses that Dr. Graham and I discussed some years ago. The bronchoscopic studies of these cases frequently give us no further information. I find that in working up these problems it is very difficult to continue with the study unless one has the sympathetic approval, let us say, of his colleagues.

By that I mean that when the patient comes to us for examination, we have complete control, and we do the various things that are mentioned here as the run-of-the-mill work, but we all know that we can't get that approval from the men who are not accustomed to the work; that is so taken for granted in a society of this kind. There is much to be done, even today, in getting our medical men to permit complete examination with x-ray, bronchoscope, and so on. It is true that once that setup is achieved—and that setup as we all know is rather universal in most of the large cities—we still have the problem to meet, and I only hope that more of our medical colleagues will see the results from such studies.

Dr. Bloch's last case particularly interested me because we have so many patients who come to us with cavities, and we are sure this has been because all the earmarks of tuberculosis are present.

DR. I. A. BIGGER, Richmond, Va.—In connection with Dr. Graham's paper I would like to present one case briefly. In the fall of 1943 I did a pneumonectomy on a 48-year-old man for what was diagnosed by several competent pathologists as adenocarcinoma. This diagnosis was based on the microscopic appearance of the tumor and on the spread to the regional lymph nodes. About 1921, one year or so after returning from World War I, this man began having recurrent pulmonary hemorrhages which were at times quite severe. After approximately ten years, he was sent to Mount Alto in Washington for a bronchoscopic examination and was told that he had a tumor in the left main bronchus.

It was understood by the patient's physician that a biopsy was done, but apparently this was not correct because I wrote to Mount Alto for the slides and was informed that tissue was not removed at the time of the bronchoscopy. This man's long history of pulmonary hemorrhages, followed by the removal of a carcinoma, strongly suggests malignant change in a bronchial adenoma.

DR. JEROME R. HEAD, Chicago, Ill.—I have looked forward very eagerly to this discussion. It is a very important question and certainly is still not settled.

Dr. Graham underestimated the force of the written word when he said that his paper in 1938 was not very well received. Since that time I have had to resist pressure to operate in these cases. I have seen relatively few benign tumors, approximately eight over a period of sixteen or seventeen years. None of them have become malignant in that time.

Dr. Bigger's contribution is important. If these tumors become malignant one would expect that in a good many of the carcinomas which we see there would be a preceding history of recurrent localized pneumonia, recurrent atelectasis, and recurrent hemorrhage. That is not common in carcinoma. When carcinoma starts the patient is usually operated upon or is dead within one year, or two or three. There is a relatively rapid progressive downhill course.

I cannot remember any case preceded by a long history of hemorrhage and recurrecent pneumonia. In regard to Dr. Bigger's statement that the tumor that he reported appeared to be carcinoma microscopically, I would say that in several of the adenomas that I have seen, the original microscopic diagnosis was carcinoma. This was reversed only when we told the pathologist, "This patient has had hemorrhage and symptoms over a period of eighteen or twenty years, and we feel that the tumor is an adenoma." He then looked back over the slide and concluded that the clinical diagnosis was correct.

The Thoracic Surgical Society may have a problem as insolvable as that of the relation of gastric ulcers to gastric cancer. I don't think it is settled yet, and I hope to hear much more discussion.

DR. LEO G. RIGLER, Minneapolis, Minn.—X-ray findings have been touched on but briefly. I should like to show a few cases to illustrate the virtue of body section roentgenography, not only in making the original diagnosis but also in following the course of events when local treatment is instituted.

For example, in a patient whose most prominent symptom was atelectasis of the lung, the planigrams show the outline of the tumor in the bronchus surrounded by a column of air. The benign bronchial tumor can be made out readily in this fashion in contrast to the carcinomatous lesion because there is often enough air remaining in the bronchus to present a contrast, whereas in carcinoma the bronchial lumen is obliterated completely. In this case, after part of the tumor had been removed by bronchoscopy, the smaller size of the lesion can be demonstrated readily in the planigrams. Later, further extirpation through the bronchoscope was accomplished, and the completely clear bronchial airway is graphically observed in the planigrams. It is possible, therefore, to see exactly what is happening until the complete aeration of the lung is restored.

The other case illustrates somewhat Dr. Brunn's comment about extrabronchial extensions of an intrabronchial adenoma. This patient had symptoms and x-ray signs that we know of for at least fourteen years prior to the time we saw her, the original lesion presenting a lobulated mass in the right superior mediastinum. It looked like a mediastinal tumor, but she had a distinct hemoptysis, which was difficult to explain on the basis of a mediastinal tumor alone. In the planigrams one may observe a rather flat, sessile type of tumor in the bronchus, which seems to extend into the trachea just beyond the bifurcation. For that reason radical treatment was not undertaken. On bronchoscopy a good deal of bleeding occurred, and the planigram illustrates very well the accumulation of blood within the bronchus which followed these procedures and which obliterated the airway completely.

I wish to comment also for a moment on Dr. Bloch's paper which was very interesting to me. We have had almost the same experience which he reports. We have done fluoroscopy on patients routinely in our outpatient clinic

for a good many years. We too have picked up occasional tumors quite accidentally in this way. I should like to direct attention to two particular points in the diagnosis of tumors of the lung which were not completely covered. One relates to the fact that films made in expiration occasionally show an obstructive emphysema which might represent the earliest stage of a bronchial tumor. In the case of a cavitating lesion, the demonstration of a bulging mass or a convexity of the mass away from the cavity, as well shown in the first two of Dr. Bloch's cases, is strongly suggestive of a neoplastic cavity in contrast with the ordinary inflammatory one, which maintains the convexity contiguous to the cavity itself.

DR. JOHN ALEXANDER, Ann Arbor, Mich.—Our pathologist, Dr. Carl Weller, has for many years insisted that the so-called adenoma is a grade I carcinoma. Clinicians went through the phases of first believing that adenomas were carcinomas and then believing that they were benign tumors. Dr. Haight and I now agree with Dr. Graham that they are carcinomas of low-grade malignancy.

In a series of thirteen patients we have had two with metastasis to the lymph node overlying the neoplasm. One of these two was in a boy 17 years of age, whose lung I removed two years ago. He had metastasis to only one lymph node, but Dr. Weller's report is that the primary neoplasm is a medullary carcinoma, grade III, arising in an adenoma.

In looking at gross sections of lungs containing so-called adenomas, I have often wondered how even such expert bronchoscopists as Dr. Holinger and Dr. Jackson can tell whether or not they can remove all the growth. In one of the cases Dr. Graham showed the intrabronchial appearance of the lesion was that of a rounded mass, and yet the sectioned specimen shows it has a very broad attachment to the bronchial wall. X-rays do not show the extent of the attachment to the bronchial wall or whether the neoplasm has grown beyond the bronchial wall, although tomographs may.

I should like to know how often Dr. Holinger and Dr. Jackson have encountered frightful hemorrhage, not mere hemorrhage, but frightful hemorrhage during attempted bronchoscopic removal of adenomas. I have had one such patient who almost lost his life from hemorrhage during an attempt to remove a part of an adenoma in order to give temporary relief of the bronchial obstruction in preparation for a pneumonectomy. I believe the risks of hemorrhage, of recurrence, and, particularly, of the transition to a more active type of malignancy than grade I carcinoma or from the fetal stage to a true carcinoma stage, together with the great ultimate risk to life of suppuration of the lung and pleura, far outweigh the risks of expertly performed lobectomy or pneumonectomy.

DR. DERYL HART, Durham, N. C.—In regard to Dr. Bloch's paper I want to call attention very briefly to fungus infections in the differential diagnosis. We have at Duke a group of medical men who are particularly interested in and alert to fungus infections. In spite of this we recently had a patient with an occlusion of the upper lobe bronchus and atelectasis in whom a diagnosis could not be made, but carcinoma was suspected.

At exploration an experienced pathologist stated that it was probably carcinoma, though he could not be sure from the sections available. A pneumonectomy was performed, the diagnosis of a fungus infection was made by pathologic examination, and blastomycetes were isolated by cultural studies. The patient was entirely relieved of the intrathoracic symptoms. No infection of the pleura occurred. However, about one month ago she was sent back to the hospital by her local physician with a diagnosis of a ruptured intervertebral disk.

On the second administration, blastomycetes were cultured from a draining sinus in the great toe and a probable diagnosis of blastomycosis of the back was made. This was confirmed by exploration.

DR. JOSEPH GORDON, Ray Brook, N. Y.—I should like to relate some of the experiences which Dr. Chamberlain and I have had recently with the cases we have been collecting in the past several years. He has had five cases at Oneonta and five cases with us at the Ray Brook Hospital in upstate New York. It seems that there is a great deal of discussion and difference of opinion, lying entirely in two directions: on one side the therapeutic management, in the other instance one has very definitely the opinion of the pathologist who views the tissue and considers it from the standpoint of those criteria which he considers make a tumor malignant.

Certainly this afternoon we have heard evidence of those criteria being present in the tumor, which do point to malignancy, and I have a few slides which I should like to show, indicating that particular point. The clinical experience, on the other hand, leaves us in doubt of the pathologist's rendered opinion because, clinically, one has in mind, when the pathologist gives us a diagnosis of malignancy elsewhere, that there is a disease or tumor and metastases which usually will cause death early. Certainly it is not true in this particular group of cases. It would seem to me that what is needed is a nice new shiny name for this particular classification of a tumor which is unlike bronchogenic carcinoma. It occurs chiefly in women in the younger age group, from 20 to 30 years of age. It may occur in very young people; however, it may be seen at very late ages, and it only causes death by the complications of pulmonary and pleural suppurative changes which result from the tumor causing obstruction.

(Slide 1.) This is the case of a 32-year-old woman who was seen in our outpatient department because of pulmonary symptoms of wheeze and dyspnea which had occurred intermittently over a long period of time. X-ray indicated changes in the pulmonary field, following which bronchoscopic examination showed the tumor, and she was advised that a lobectomy was indicated. On the basis of the collected experiences of other people the complications which result in these cases are not only most debilitating, but may ultimately lead to death, hence the recommendation.

(Slide 2.) This is the appearance of the tumor, and cystic dilatations can also be seen. It has the characteristic collar button appearance. The major portion of the tumor is extrabronchial, and it was these dilatations which made us wonder about the possibility of its being embryonal in origin as Dr. Graham has suggested. But invariably these dilatations occur distal to the tumor rather than elsewhere in the lung.

(Slide 3.) This is the case of a 21-year-old girl. The point that has been made before and is brought up in this case is that the condition in these people is erroneously diagnosed as tuberculosis or carcinoma or pneumonia. This girl was in a sanatorium for two years with diagnosis of pulmonary tuberculosis before transfer to Ray Brook for surgery. She was operated upon and the tumor was removed; here again you see the smallest portion of the tumor present in the bronchus.

(Slide 4.) This is the case of a 47-year-old woman who had an x-ray film showing this shadow. She previously had symptoms of respiratory infection associated with fever over a long period of time. Bronchoscopy was done and biopsy was reported as adenocarcinoma elsewhere. She was transferred and operated upon for clinically diagnosed adenoma. The lobe was removed, and here again we see a small portion of the tumor appearing in the bronchus and a dilatation distal to it. Microscopic examination showed the same histological appearance which was shown in the other case.

One of the points which was mentioned particularly by Dr. Alexander is noted in the following case. The sclerosis and instances of horrible bleeding which occurred in this case show the end results of a tumor which has existed fourteen years, suppurating the entire lung. The tumor was biopsied; bleeding occurred slowly over a period of several hours, but did not seem to be alarming. A blood clot formed on the wall of the trachea which was suddenly aspirated and the patient died immediately of asphyxia.

(Slide 5.) This shows the irregular histologic appearance which is not diagnostic.

(Slide 6.) This is a section showing the appearance of bone occurring, which is incidental.

(Slide 7.) This is evidence of lymph node involvement which was present in three of the four cases examined histologically.

MAJOR M. DAWSON TYSON, McKinney, Texas.—I want to show briefly one case of bronchial adenoma which to me illustrates the difficulty of determining what is going on in the lung beyond the tumor as pointed out by Dr. Alexander. Also, the rationale for radical surgery is brought out by this case. The lesion occurred in a 27-year-old telephone operator with a two-year history of intermittent pneumonia. She at no time had productive cough except during the attacks of pneumonia, and she had no hemoptysis at any time.

(Slide 1.) This was taken during one of the attacks of so-called pneumonia and shows collapse of the right lower and middle lobes. One month later the lobes have re-expanded. Four months later she shows atelectasis of these lobes again. Bronchoscopy was done and a large tumor was found in the right stem bronchus. Biopsy was taken and benign adenoma diagnosed, though the pathologist thought the lesion was quite active.

Thoracotomy was decided upon as the safest method of treatment in this case. From the standpoint of contamination, it was thought safer to transect the bronchus without preliminary bronchoscopic removal of the tumor, since the obstruction was complete and there was no sputum. Preliminary pneumothorax was instituted and a complete collapse of the right lung was obtained for one week prior to operation.

In opening the pleura it was found that the lung was completely atelectatic and there were only a few delicate, avascular adhesions present. When the hilum was palpated, the tumor mass could be felt protruding through the posterior surface of the main bronchus. It was seen that there was no anatomic separation between the upper and middle lobes. The lower and middle lobes were indurated throughout. A total pneumonectomy was decided upon because it was felt that if the tumor were to be completely removed, the incision in the bronchus would come so close to the upper lobe bronchus that closure of this structure would be inadequate or impossible. Also, if total pneumonectomy were not done, transection of infected lung tissue would have to be carried out, which would add to the risks involved. In addition, there was still no complete assurance of the benign character of the growth. Therefore, total pneumonectomy was carried out.

(Slide 2.) This view is looking down the bronchus at the tumor. The upper lobe bronchus is seen at the top of the slide.

(Slide 3.) This shows the extrabronchial extension of the tumor on the outside of the bronchus.

(Slide 4.) This is a picture of a cross section of the lung showing the marked bronchiectasis of the middle and lower lobes.

(Slide 5.) This x-ray picture was taken just under one year postoperatively and shows the compensatory changes. The operation was done in February, 1940. The patient has been followed closely for four years and has been found able to

keep on with her work. She does complain of a little whistling of air around the angle of the trachea when she gets out of breath walking up a hill. Interestingly enough, her vital capacity which was 70 per cent of normal before operation and was 60 per cent in succeeding weeks, has now risen to 90 per cent of normal. Last month she delivered a normal offspring at term (her first). There were no complications.

DR. CHEVALIER L. JACKSON, Philadelphia, Pa.—I have been very much interested in Dr. Graham's embryological observations concerning these tumors. One of our clinical observations is that they always, or almost always, originate at a bronchial spur. I would like him to comment just a moment on the connection between that observation and his embryological view of the development of these tumors, when he closes the discussion.

We all seem to be pretty well in agreement as to the importance of bronchial obstruction and its consequences in these tumors, and I will not say anything more about that. We do seem to be very interestingly at variance, however, as to the malignancy of these tumors and the bearing of their malignancy or lack of it on their management. As stated in our paper, we feel that there is no inherent tendency, in these tumors, to malignancy. We go that far, and furthermore, we think that the incidence of malignancy must be relatively low from the study of our clinical material. From the tabulation of our twenty cases I might read the ages, or rather the duration of observation: two years, two years, six months, twenty years, three years, seven years, twenty years, fourteen years, eight years, four months, ten years, twelve years, twenty years, thirteen years, and three years. If these cases are all of this category, be they called bronchial adenoma or by the "new shining name" that Dr. Gordon thinks we may find, it is interesting that the duration of observation in so many of the series of cases was so long. Dr. Adams has made a very important point in his plea for accurate pathologic diagnosis, because without that we certainly don't know what we are talking about. In the work sheet referred to in our paper we listed the different diagnoses made at various times in each of these cases. In eight of the cases I marked the diagnosis "okay" to signify that there had been no difficulty in making the diagnosis; but in eight other cases a great variety of diagnoses had been mentioned, at one time or another; as a matter of fact, these were for the most part the earlier cases. That is just a further evidence of the unquestionable difficulty in making this histopathologic diagnosis: I think that, as Dr. Gordon has said, this is a problem on which the clinicians and the pathologists must work together. We will not get anywhere if we listen to a man talk for fifteen minutes about what happened to a particular patient, taking for granted that it was what he said it was. If it were not that sort of tumor, then what he says about it does not mean anything. I am not talking to any individual at all. This might apply to myself or to some of the rest of us, but it does emphasize the importance of accurate histopathologic diagnosis when we are talking about tumors.

Dr. Adams made an excellent point, which brings the light to us all, in showing why the thoracic surgeons are so thirsty and hungry for these cases! If they can get 99 per cent cures of these tumors by lung resection of course they will want to operate upon some of them, and if they have them listed properly with regard to histopathologic diagnosis, I am ready to congratulate them!

Dr. Alexander asked two questions: first, as to how we could tell when we see the proximal surface of a bronchial tumor whether or not we can remove the whole thing bronchoscopically. We cannot tell. As we remove a part of the tumor, however, and get enough by-passage to get a small bronchoscope beyond it, and see the spurs further down in the bronchial tree, we can form an approximate idea of its size and then decide. In the one case I illustrated here by the

gross specimen, I never got beyond the tumor with the bronchoscope and that was one of the cases in which we felt pneumonectomy was indicated. The second question, "How often does frightful hemorrhage result?" is rather an important one. I can say that in our cases, so far, we have not had one case of "frightful" hemorrhage from an adenoma. I do not say we will not have one, but I do think one way we can avoid hemorrhage or, let us say, minimize the risk from hemorrhage, is not to try to do too much at one sitting; biopsy is enough the first time, and then electrocoagulation, subsequently alternating forceps removal with electrocoagulation at appropriate intervals, removing the obstructive lesion in a series of bronchoscopies, rather than trying to cure in one treatment.

DR. PAUL H. HOLINGER, Chicago, Ill.—There was no discussion of my presentation which was, in fact, simply a motion picture. However, I would like to take this opportunity to enter the discussion of bronchial adenomas. When there is such a great variation of opinion I believe we must analyze each other's sections and see if we are all talking about the same thing. A tumor called an adenoma by one pathologist and an adenocarcinoma by another will probably show malignant characteristics more readily than a tumor all agree to be an adenoma. The variation in the histologic picture of these tumors suggests the need for their gradation in a manner similar to the gradation of malignant neoplasms. This would have diagnostic and prognostic value and could be one of the criteria upon which the subsequent treatment could be based. I realize, of course, as Dr. Graham has shown, that tissue from various parts of the tumor might give extreme variations in gradation. Nevertheless, if one takes repeated biopsies from a tumor in an effort to open a bronchus, one can get fairly representative sections.

In our experience the question of hemorrhage is one which influences the choice of therapy. If a tumor has a tendency to bleed profusely when efforts are made bronchoscopically to free the affected bronchus, bronchoscopic removal is discontinued and surgical resection is advised. I believe that those with a marked tendency toward bleeding are definitely not bronchoscopic problems.

DR. EVARTS A. GRAHAM, St. Louis, Mo.—Dr. Adams says that several of his cases had metastases to the lymph glands, but that of course they were not malignant tumors. I do not understand what his conception of a malignant tumor is, and if the Chairman would permit it, I would like to have him state his criteria of malignancy. In regard to the question of time, of course these tumors are slowly growing. It is rare to find any mitotic figures. They are of necessity, therefore, slowly growing tumors, and it is not surprising that occasionally one gets a history of twenty years or longer before such a tumor has shown invasive qualities. I still believe that Virchow was right when he stated that invasion is a criterion of malignancy.

Dr. Womack and I have called attention to certain similarities of these tumors to those of the salivary glands. In the case of tumors of the salivary glands there is often a long latent period before invasive qualities are evident. Also, there are often found various kinds of tissues in both groups of tumors.

I am very glad of the confirmation of our ideas by Dr. Alexander.

I do want to say, however, in order to avoid being misunderstood, that of course these tumors are not all malignant when first seen. I am talking only about the fact that they are potentially malignant. What makes a tumor malignant is something that nobody knows at the present time. That is to say, what makes a change from a so-called benign state or an innocent state into a malignant state is something that no one can properly explain at the present time. But I am talking only about the fact that something does happen to some of these tumors to make them take on an invasive quality, and therefore, in my opinion, they become malignant when they have taken on that invasive quality.

We have heard a good deal about negative findings. I do not think that negative findings are of very great significance. One positive finding, in my opinion, of the fact that these tumors become malignant is worth infinitely more than a lot of negative findings. Of course we do not know at the present time, and I think it is very important for us to find out by repeated discussions of this question, about what the percentage chance of one of these tumors is of becoming malignant. That is something that I do not know, but I do know that we have had more than ten cases now in which there have been regional or distant metastases from tumors which have begun as adenomas with a long preceding history. Dr. Adams and Dr. Bloch have reported five more. There have been three from the German literature, and so on, and today we heard from Dr. Gordon about four of his cases with lymph gland involvement. Dr. Bigger's case, I believe, was certainly one of these adenomas which became malignant. I would like to know how many examples are needed before one accepts the idea that these tumors are potentially malignant.

DR. RALPH ADAMS, Boston, Mass.—Anyone could predict the outcome of a sparring match between Dr. Graham and myself on pathology. Our pathologists made the pathologic classification of adenoma and included those cases which showed local metastases to glands about the adenoma. In the subsequent follow-up of those cases, in all instances, from three to five years, we have had no instance in which the behavior suggested that the adenoma was originally malignant in the sense that a carcinoma is admittedly malignant. Maybe three analogies will be informative.

There is adenoma of the thyroid which we hardly need to discuss further. It is not malignant but certainly it can become malignant. The so-called Meigs tumor characteristically shows signs of metastasis, by pleural effusion, if pleural effusion be interpreted as a sign of metastatic irritation; yet it is not a carcinoma. Tabes mesenterica typically exhibits enlargement of the glands at the base of the mesentery, and yet there again it is not malignant in the sense that a carcinoma is malignant.

Dr. Jackson said 99 per cent. I am afraid my Southern accent, or remnant of it, was misinterpreted. What I meant to say was 90 and 9 per cent because ten divided by eleven gives ninety and nine; that still is not bad.

HAMARTOMA (OFTEN CALLED CHONDROMA) OF THE LUNG

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DURING the past year, three benign pulmonary tumors which were removed surgically at the Mayo Clinic were strikingly similar and unusual. These tumors contained essentially the same elements. Because of the variety of tissues, both epithelial and mesothelial, in these tumors it was suggested that they were teratomas. Closer analysis disclosed that all tissues in the tumors corresponded with those found normally in the bronchi, although lacking in any orderly arrangement. Such neoplasms of the lung have been described in the literature. They are supposed to be the result of abnormal development of the bronchial anlage; therefore, they have been called hamartomas (to fail, to err). The term was coined by Albrecht,[1] in 1904, who stated, "hamartomata are tumor-like malformations in which occurs only an abnormal mixing of the normal components of the organ. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation, or may comprise all three. The deduction to be drawn from histologic examination of these formations is that they have originated in an abnormal mixing of the elements or from disturbance of their development." Albrecht did not apply this term specifically to the type of pulmonary tumor under consideration but designated such tumors as hemangioma of the liver as hamartomas.

In the earlier reports on this condition, cartilage was the only recognized component of the tumor. The tumor was referred to as chondroma of the lung. In 1883, Chiari[2] reported two cases. In addition to cartilage, fat and glandular epithelial elements were present in both tumors. He suggested the term lipochondro-adenoma. Since Albrecht's description of the general group of hamartomas, they have been most commonly designated as hamartomas or hamartochondromas, although some writers still employ the older terminology.

It cannot be denied that pure chondromas of the lung occur, although we have had no experience with them as such. As has been stated, cartilaginous tumors in the lung are occasionally referred to as chondromas when other elements such as epithelium, fat, and smooth muscle are incorporated in the tumor. These are not true chondromas.

We have confined the use of the term "hamartoma of the lung" to a specific type of tumor of the lung which has a characteristic morphologic appearance; this is a solid tumor of the bronchus which consists

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of benign mesodermal and benign epithelial elements. Most observers who have written on this subject in the literature have confined their remarks on hamartoma of the lung to this type of tumor. There is, however, one notable exception.

In 1938, Womack and Graham[3] recalled the term hamartoma used by Albrecht, which he had coined to designate a tumor of the liver. It was their opinion that many of the tumors of the lung result from the failure of embryonic bronchial buds to develop into normal structures. Originally these buds, of course, consist of mesoderm and entoderm. They proposed that two main groups of pulmonary tumors can be considered as occurring from a failure of the bronchial buds to develop into the orderly arrangement of tissues regarded as normal. These two groups are (1) those in which the mesodermal elements predominate and (2) those in which the entodermal (or epithelial) elements are dominant. The former group, according to their idea, includes such tumors as those which are called chondroma, osteoma, fibroma, lipoma, angioma, myxoma, and sarcoma. The second group is illustrated chiefly by the so-called adenoma. Since in all these tumors there is often a mixture of tissues from different embryonal elements and since some, especially the adenomas, display in their structure and growth some of the characteristics of the "mixed tumors" of the salivary glands and kidney, they suggested that all of the pulmonary tumors which supposedly arise from embryonal bronchial elements be designated as "mixed tumors of the lung." They called attention to the fact that often one finds in a bronchial adenoma abnormal cartilage and even bone.

We are not including adenomas of the lung in our discussion of hamartomas, but are conjuring the use of the term hamartoma of the lung to designate that group of tumors described previously.

The subject has been reviewed by Hickey and Simpson[4] (1926), by Verga,[5] (1932) and by Goldsworthy[6] (1934). Hickey and Simpson, in 1926, collected thirty-eight cases of chondromatous tumors from the literature and reported two which they had observed. Verga, in 1932, collected sixty-one cases, including three of his own. From this time until 1941, twelve cases of hamartoma of the lung have been reported in which histologic proof of the tumor was obtained (Sherwood and Sherwood,[7] one case; Peters,[8] one case; Benninghoven and Peirce,[9] one case; Jaeger,[10] five cases; Livingston,[11] one case; Edling,[12] one case; Roux-Berger and Debroise,[13] one case; and Mallory,[14] one case). In addition, in this period three cases of polypoid tumors of the bronchus of a chondromatous nature have been reported by Moore,[15] Gebauer,[16] and Davidson,[17] but it would seem that neoplasms of this type should not be included with hamartomas.

In the majority of the cases reported in the literature, the tumor was found incidentally at necropsy. Symptoms referable to the tumor in the lung were present in only a few cases. In only one or two instances

was the roentgenographic appearance sufficiently characteristic to permit an antemortem or preoperative diagnosis to be made. Furthermore, there are only a few reports of the successful surgical removal of this type of tumor.

Sherwood and Sherwood[7] (1932) reviewed forty-one cases reported in the literature and found that twenty-four of the patients were men and seventeen were women. This suggests that there is nothing significant about the incidence of this tumor in the two sexes. In twenty of thirty-two cases, the age of the patients at the time of discovery of the hamartoma was more than 50 years. In the reported cases, the tumors were situated in the pulmonary parenchyma; in the majority of cases the tumor was situated beneath the pleura. Hickey and Simpson[4] found that the tumor was situated in close proximity to the pleura in twenty-six of thirty cases; in the four remaining cases, it was situated near the root of the lung.

Benninghoven and Peirce,[9] (1933) reported two cases of chondromatous tumors of the lung. In one of the cases the tumor was removed surgically. In the other case, the diagnosis was not proved by histologic examination. They said that the diagnostic features of this type of tumor are: (1) an abnormal mass of great density is surrounded by normal lung; (2) the tumor has a sharply defined and lobulated border; (3) within the tumor are scattered areas of greater density resembling bone. Hickey and Simpson[4] said that in the course of roentgenographic examination the tumor usually was mistaken for hydatid cyst.

In some of the reported cases the tumors have been as small as a bean; in other cases, they have filled the entire thorax. The tumors usually have been lobulated, which has been explained by the multiple islands of cartilage representing multiple centers of growth. The cartilage frequently had undergone calcification or even ossification. In cases in which ossification was present, bone marrow cavities could be demonstrated. In many cases cystlike spaces were present between the islands of cartilage. The tumors were sharply demarcated from the surrounding pulmonary tissue.

Another feature of these tumors is that, although the surrounding lung may be quite mottled with anthracosis, deposits of coal dust never are encountered in the tumors.

In many of the cases reported in the literature, histologic examination revealed that the tumor was composed entirely of cartilage. Since Albrecht's description of hamartomas, an increasing number of these tumors has been shown to be made up of mixed elements. In most cases, cartilage has appeared to be the most prominent element. This has usually been hyaline cartilage, although it occasionally has been fibrous and even elastic. Multiple islands of cartilage are scattered throughout the tumor; each island is surrounded by perichondrium. Calcification and formation of bone have been observed commonly in the cartilage. According to Hickey and Simpson, fat has been present in the tumor

in one-half the reported cases. Epithelial elements frequently have been present, and mucous cysts often have been observed. The epithelial lining of these cysts, although usually nonciliated, has in certain cases been ciliated. Hickey and Simpson concluded that "the components of these tumors constitute a bronchial complex, with representatives of all the histologic elements which go to make up mature bronchi."

Malignant change in this type of tumor is apparently a rare occurrence. Greenspan[18] (1933) reported a case of osteochondrosarcoma of the lung in which metastasis occurred. It is possible that such a neoplasm was primarily a hamartoma. On the other hand, it seems possible that such a tumor was a true osteochondroma that had undergone malignant change.

MATERIAL

This paper is based on twenty-three cases of hamartoma of the lung that were observed at the Mayo Clinic. In three of these cases the tumor was removed surgically. In the remaining twenty cases, the tumor was found at necropsy.

It would appear that this tumor is much more common than has previously been thought. The twenty cases in which the tumor was found at necropsy were part of a series of 7,972 consecutive cases in which necropsy was performed. The incidence of this tumor in this series of 7,972 cases was 0.25 per cent. It would seem probable that it is even more common than this figure would indicate. Even in a careful examination of the lungs, a few of these tumors will be overlooked because of their small size and subpleural situation.

In the twenty-three cases, six of the patients were women and seventeen were men (Table I). The ages of the patients ranged from 21 to 85 years.

REPORT OF CASES

We wish to report briefly three cases in which the tumor was removed surgically. Symptoms referable to the tumor in the lung were present in only one of these cases (Case 3). In all, the tumor was recognized roentgenographically.

CASE 1.—The patient was a woman, aged 47 years. For nine months before she came to the clinic, she had had symptoms of a scalenus anticus syndrome on the right side. A right anterior scalenectomy and cervicothoracic sympathectomy were performed. Roentgenographic examination revealed a tumor in the anterior part of the thorax to the right of the mediastinum (Fig. 1). Through a right anterior transpleural approach the tumor was located subpleurally in the lower part of the right upper lobe. It was 4 cm. in diameter (Fig. 2). The tumor was excised. The patient made an uneventful recovery and two months later there were no symptoms referable to the thorax.

CASE 2.—A man, aged 37 years, was rejected by the Army because of a mediastinal tumor. He had no symptoms referable to the thorax.

TABLE I

CLINICAL AND PATHOLOGIC FINDINGS IN CASES OF HAMARTOMA OF THE LUNG

CASE	SEX	AGE (YR.)	SITE	SIZE (CM.)	HISTOLOGIC APPEARANCE
1	F	47	Right upper lobe	4.0	Islands of cartilage, bone, epithelium (ciliated), fat, smooth muscle, and myxomatous connective tissue
2	M	37	Right lower lobe (hilus)	4.0	Islands of cartilage, ciliated epithelium, myxomatous fibrous tissue, and smooth muscle
3	F	21	Right upper lobe (hilus)	9.0	Fibrous myxomatous tissue and epithelium; no cartilage
4	M	62	Lung	0.5	Lobulated island of cartilage, epithelium (nonciliated), myxomatous fibrous tissue, and fat
5	M	69	Left upper lobe	1.8	Lobulated island of cartilage, epithelium (nonciliated), myxomatous connective tissue, and fat
6	F	57	Left lung	0.4	Islands of cartilage, nonciliated epithelium, myxomatous connective tissue, and fat
7	M	75	Right lower lobe	3.0	Islands of cartilage, few epithelial cysts lined by cuboidal epithelium, myxomatous connective tissue, and fat
8	M	41	Right lower lobe	0.4	Lobulated island of cartilage, cuboidal epithelium (nonciliated) at edge of cartilage, and myxomatous connective tissue
9	M	61	Left lower lobe	0.3	Irregular island of cartilage; myxomatous connective tissue forming perichondrium
10	M	62	Right lower lobe	0.4	Islands of myxomatous connective tissue; epithelial lined glands (no cilia) at edge, and fat
11	M	71	Right lower lobe	0.4	Islands of cartilage and bone; epithelium (nonciliated) forming glands at edges in fat; fibrous connective tissue
12	M	61	Right upper lobe	1.2	Islands of cartilage, myxomatous connective tissue, and epithelium (ciliated)
13	M	65	Lung	0.5	Islands of cartilage, myxomatous connective tissue, ciliated columnar epithelium, and fat
14	F	34	Left lower lobe	1.0	Islands of cartilage, myxomatous connective tissue, epithelium (nonciliated), and fat
15	F	73	Right upper lobe (hilus)	1.3	Islands of cartilage and fibrous myxomatous tissue forming cartilage; ciliated columnar epithelium
16	M	68	Left upper lobe (base)	1.1	Islands of cartilage and myxomatous connective tissue, glandular epithelium, and fat
17	M	63	Lung	0.3	Islands of cartilage and myxomatous connective tissue, glandular epithelium (nonciliated)
18	M	67	Left lung	0.2	Irregular islands of myxomatous connective tissue (no cartilage) and ciliated glandular epithelium
19	M	71	Left upper lobe	0.4	Cartilage and myxomatous connective tissue, glandular epithelium (nonciliated), and fat
20	M	77	Right lower lobe	1.6	Islands of cartilage and myxomatous connective tissue, many glands (nonciliated), some cystic
21	F	68	Right lower lobe	0.7	Islands of cartilage, myxomatous connective tissue, and fat; no epithelium
22	M	85	Right middle lobe	0.6	Islands of cartilage, myxomatous connective tissue, fat, and epithelium
23	M	80	Left upper lobe	0.7	Islands of cartilage, fat, myxomatous connective tissue, and epithelium

Roentgenographic examination revealed a round tumor which appeared to be situated in the middle mediastinum just posterior to the heart on the right side (Fig. 3). The tumor contained calcium. The right

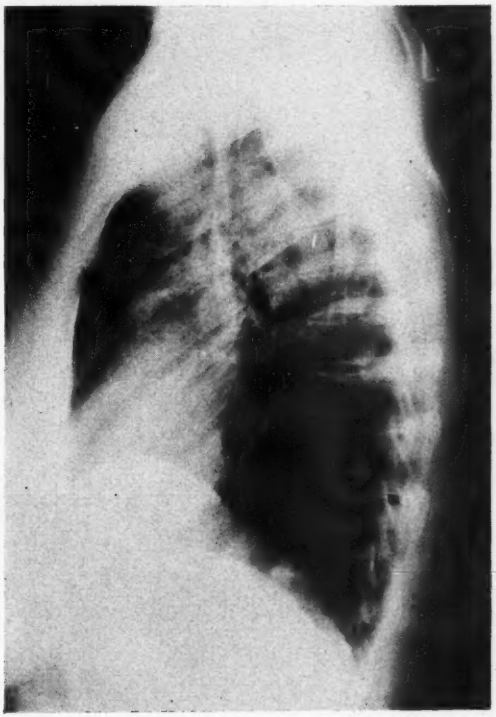

Fig. 1.—Lateral roentgenogram showing hamartoma in anterior portion of right side of thorax (Case 1).

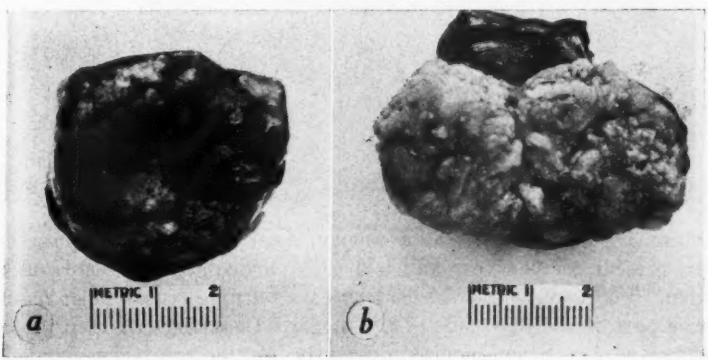

Fig. 2.—*a*, Gross appearance of tumor removed (Case 1); *b*, cut surface of tumor.

lower lobe was removed. The tumor was situated subpleurally in the interlobar portion of the lung near the hilar vessels. It was 4 cm. in diameter. The patient had an uneventful convalescence.

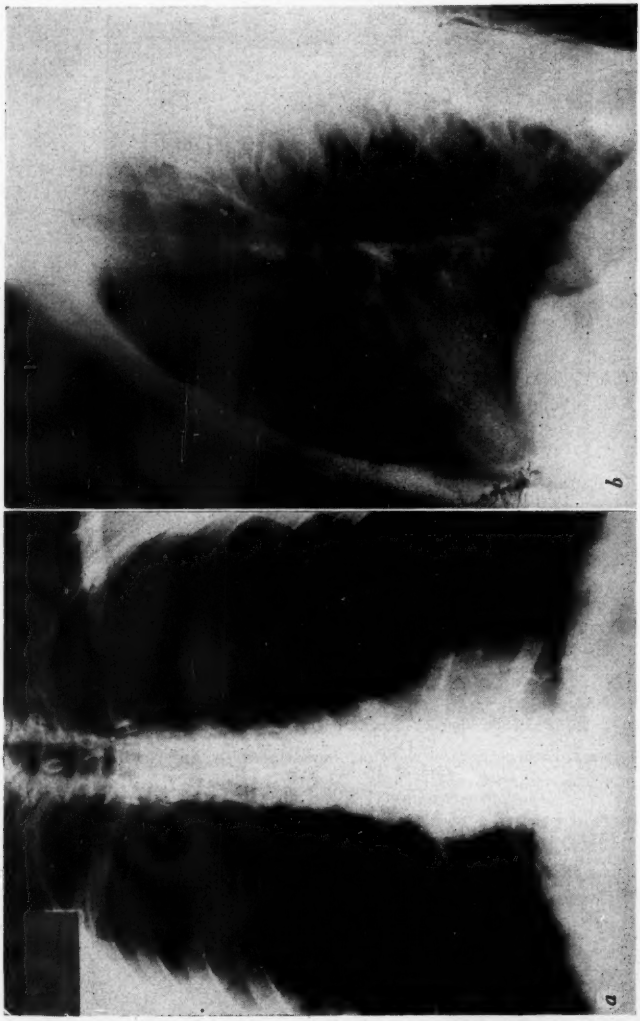

Fig. 3.—Hamartoma in right side of thorax protruding from behind the mediastinal shadow (Case 2); areas of calcification are visible; *a*, anteroposterior view; *b*, lateral view.

Case 3.—The patient was a woman, aged 21 years. Dyspnea had been present for one year and had been particularly noticeable on exertion. For two months she had noted a burning sensation in the anterior part of the right side of the thorax. Coughing had been present for two weeks. Seven months previously, routine roentgenographic examination had revealed a tumor in the right lung.

Roentgenographic examination at the clinic disclosed a well-circumscribed tumor of the right lung, which was situated near the hilus (Fig. 4). Bronchoscopic examination did not disclose any abnormality. Pneumonectomy was performed on the right side. The tumor

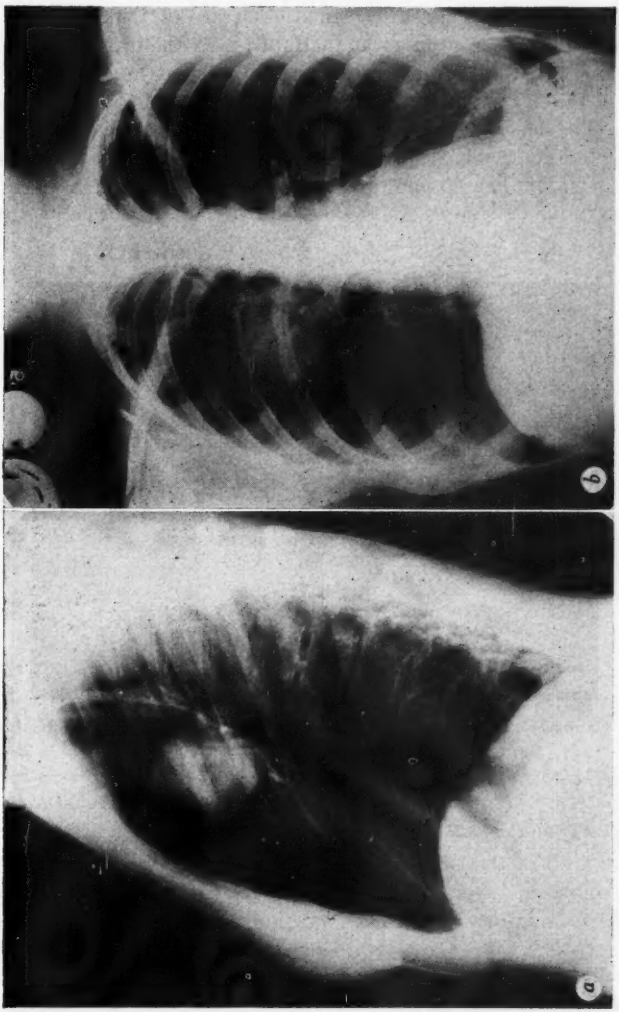

Fig. 4.—Hamartoma in the hilus of the right lung (Case 3); *a*, anteroposterior view; *b*, lateral view.

was situated in the central part of the right lung and had involved one of the secondary bronchi of the upper lobe (Fig. 5). Recovery was uneventful.

PATHOLOGIC FINDINGS

It was not possible to determine the exact site of the tumor in all cases because this was not stated in some of the cases in which the tumor

was found at necropsy. All of the tumors were situated in the parenchyma of the lung; none were in the mediastinum. In most of the cases in which the site of the tumor could be determined, the tumor was situated subpleurally; in some cases it was at the costal surface of the lung, in other cases it was in the interlobar portion of the lung, while in still others it was on the diphragmatic surface of the lung. In three cases, the tumor was situated at the hilus, near the large vessels of the lung. In twelve cases it was situated in the right lung, in eight cases it was in the left lung, and in three cases the site of the tumor was not stated. The lobe that was involved could be determined in eighteen cases. The tumor was situated in the right upper lobe in four cases, in the right middle lobe in one case, in the right lower lobe in seven cases, in the left upper lobe in four cases, and in the left lower lobe in two cases.

Fig. 5.—Hamartoma of right lung (Case 3); the tumor has involved the bronchus.

The largest hamartoma observed in this series of cases was 9 cm. in diameter. Those that were found at necropsy were from 0.2 to 3 cm. in diameter; most of them were less than 1 cm. in diameter.

Grossly, all of the tumors were whitish and sharply demarcated from the surrounding lung. Frequently, the cut surface appeared lobulated (Fig. 6). In an occasional case, calcium was scattered throughout the tumor. In one case (Case 3), a bronchus was involved. Although the involved bronchus was narrowed, there was no evidence of bronchiectasis or atelectasis distal to the site of involvement.

The histologic findings in the twenty-three cases are listed in Table I.

Islands of cartilage (Fig. 7) were found in all except three of the tumors. These islands of cartilage were separated from one another by bands of connective tissue. As these bands of connective tissue had undergone mucoid degeneration, they somewhat resembled primitive

mesenchyma. This connective tissue was performing the function of the perichondrium (Fig. 8) and spindle cells could be seen changing into chondroblasts. The connective tissue (Fig. 9) was present in all cases. Glandular epithelium was present in twenty-one of the twenty-three tumors. The glands were lined by a single layer of either columnar or cuboidal cells (Fig. 10) which were producing mucus in variable quantities. In six cases, definite cilia (Fig. 11) could be demonstrated along the free border of the epithelium. In these cases, not every gland

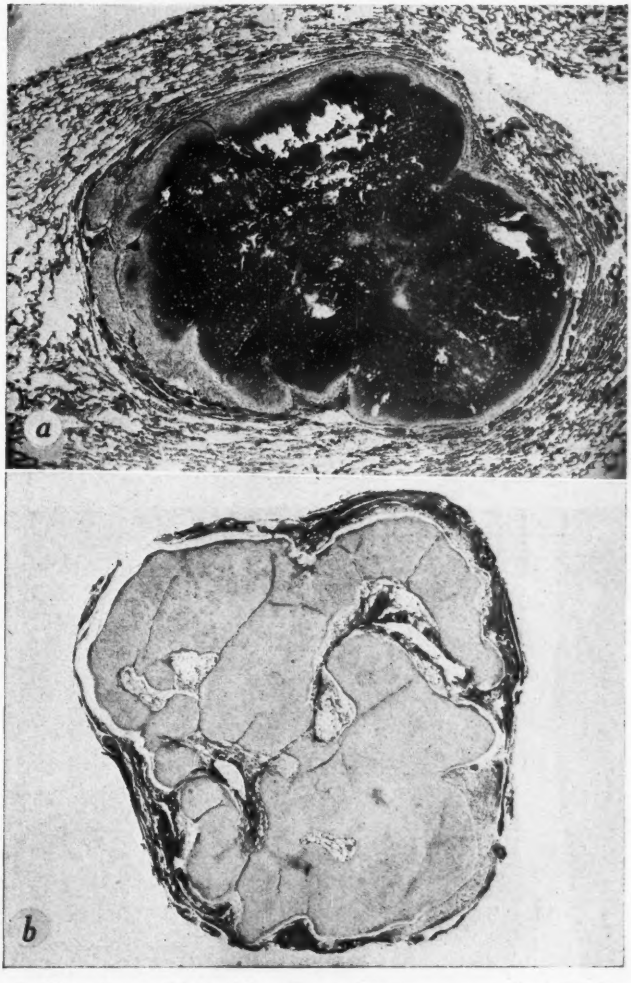

Fig. 6.—Hamartoma of lung (Case 7). *a*, The tumor was situated subjacent to the pleura and was sharply demarcated from the surrounding lung (×14); *b*, in Case 20 the tumor contained lobules of cartilage (×10).

had cilia. In several cases, many ciliated cells were observed; in others, only a few were present. The glands that were lined with epithelium bore a distinct resemblance to those lining the bronchus. When present in these tumors, they were most numerous at the edge and seemed to be growing into the tumor along the strands of connective tissue. Fat was observed in fourteen cases. This was adult fat and was rarely present

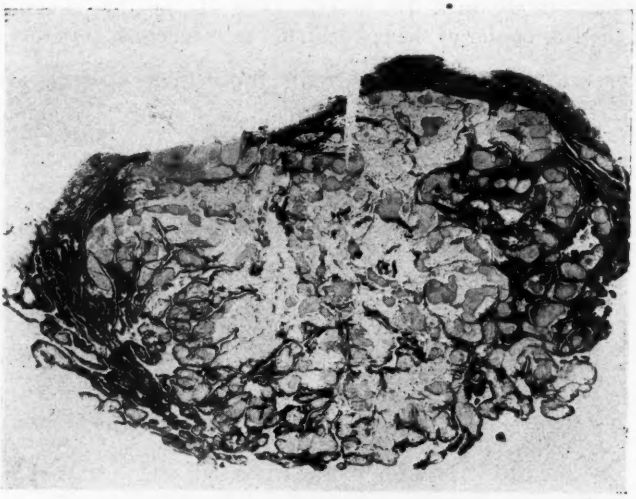

Fig. 7.—Section of entire tumor (Case 1); individual islands of cartilage are visible (×3).

Fig. 8.—Section of hamartoma (Case 2); islands of cartilage are surrounded by fibrous myxomatous tissue which is acting as perichondrium; glandular epithelium is present in the bands of connective tissue (×60).

in any large quantity. When present, it was intermingled with the bundles of connective tissue. Smooth muscle was present in two tumors, and bone (Fig. 12) was found in two tumors.

SYMPTOMS AND DIAGNOSIS

From a review of these twenty-three cases of hamartoma of the lung, as well as of those reported in the literature, it is apparent that this

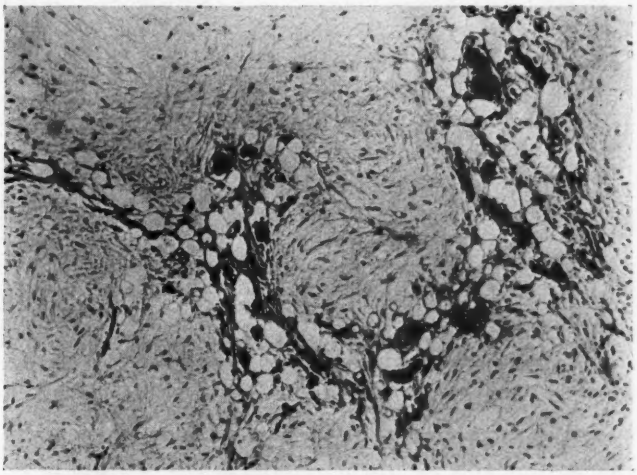

Fig. 9.—Section of hamartoma (Case 9); myxomatous tissue contains a few adult fat cells (×95).

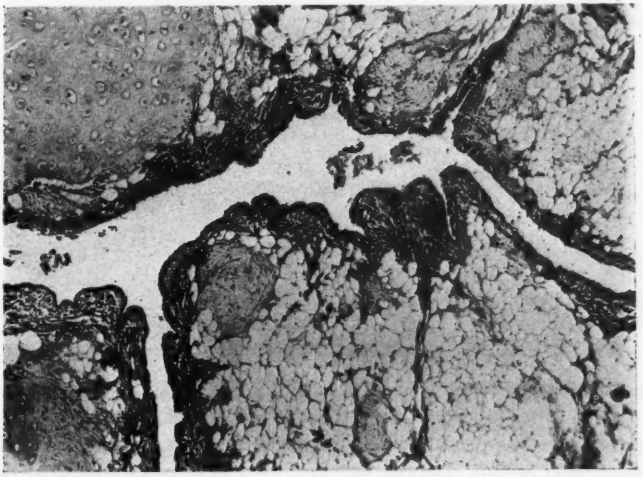

Fig. 10.—Section of hamartoma (Case 1) showing branching glands lined with cuboidal epithelium and surrounded by myxomatous tissue, cartilage, and fat; papillary infolding is visible (×60).

tumor seldom produces symptoms of clinical importance. In only one of our three cases in which the tumor was removed surgically were there any symptoms referable to the tumor. Since this tumor is relatively

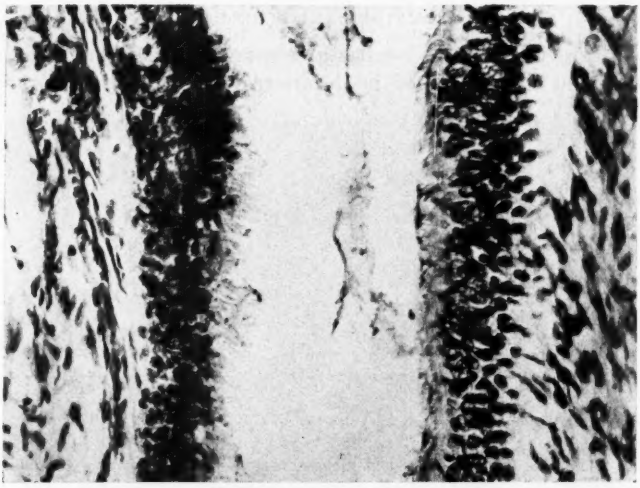

Fig. 11.—Glandular epithelium with cilia (Case 12) (×285).

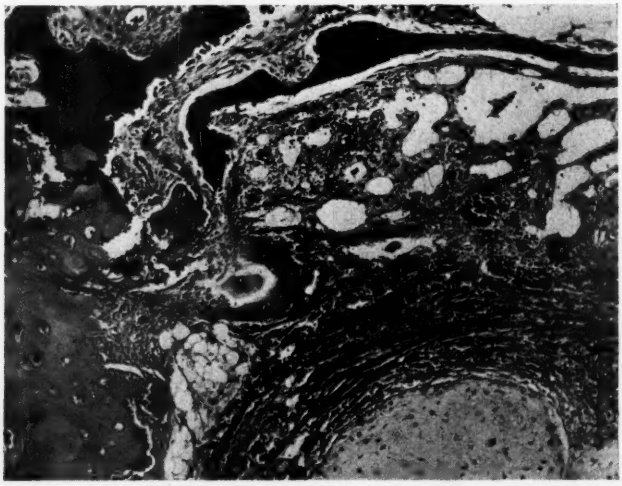

Fig. 12.—Islands of cartilage that have undergone partial ossification (Case 1); these islands are separated by fat and fibrous tissue (×60).

asymptomatic and produces few physical findings, it seems likely that in most of the cases the tumor will be discovered in the course of routine roentgenologic examination of the thorax. The roentgenographic characteristics of this tumor are of particular significance because there is no

other means of making a diagnosis. Since the tumor usually is situated in the periphery of a pulmonary lobe, bronchoscopic examination is not of much value but should be done to rule out other pulmonary lesions. Roentgenologically, this tumor is manifested by a dense shadow which has round or lobulated borders and is surrounded by normal pulmonary markings. In most cases, there are scattered areas of increased density within the mass, indicating calcification. The peripheral site of the tumor may be of some diagnostic significance but cannot be depended on, as was illustrated in Case 3. Pulmonary lesions that must be considered in the differential diagnosis include primary carcinoma of the lung, single metastatic carcinoma of the lung, tuberculoma, Ghon complex, hydatid cyst, other cysts of the lung, encapsulated interlobar effusion, and empyema. It usually is impossible to do more than suspect that the roentgenographic picture is produced by a hamartoma. Accurate diagnosis requires microscopic examination of the tumor.

SURGICAL TREATMENT

Although hamartoma of the lung is a benign, slow-growing tumor that usually is asymptomatic, we believe that it should be removed surgically. There are no good tumors and any growing tumor is a menace that should not be tolerated, provided, of course, that it can be removed with reasonable risk. Furthermore, as previously noted, one is limited diagnostically by the roentgenographic appearance of the lesion. There are other more serious lesions of the lung which cannot be distinguished with certainty before operation. In the case of the small peripherally situated tumors, local excision with minimal sacrifice of pulmonary tissue can be carried out satisfactorily. This was possible in Case 1. Lobectomy, or even pneumonectomy, may be necessary for larger, centrally situated tumors.

The operation should be performed with intratracheal positive pressure anesthesia. The approach may be governed by the situation of the tumor but we prefer a posterolateral incision curving around the tip of the scapula. Resection of a long segment of the fifth, sixth, or seventh rib will afford adequate exposure in most instances. Additional exposure can be obtained by resection of short segments of adjacent ribs posteriorly, if necessary. On palpation, this tumor is hard, round, or lobulated, and is surrounded by normal lung. The tumor is usually subpleural but there is no pleural involvement. The extent of pulmonary resection is determined by the situation and the size of the tumor. Frozen sections of the tumor should be examined microscopically immediately so that the nature of the tumor can be determined without question. This is important because, as we have already pointed out, it is impossible to make a positive preoperative diagnosis, and if the lesion should not prove to be a hamartoma, more extensive pulmonary resection might be necessary.

COMMENT

In our experience with tumors of the lung, we have found no other tumor which approximates the pathologic appearance of hamartoma. In none of our cases has there been any suggestion of malignant transformation. It seems likely, as has been suggested, that this tumor originates from the bronchial anlage. These tumors have many and occasionally all the elements of the adult bronchus, although with an abnormal admixture. Even bone was found in a few of the tumors. This frequently is found in the bronchus of an adult. It seems probable that the tumors which in the older literature were regarded as pure chondromas were really hamartomas in which the heterologous elements were not recognized. Hamartomas should not be regarded as true teratomas. They have only bronchial elements and they are not situated in the mediastinum where intrathoracic teratomas are found. Roentgenologically, when hamartomas are small, they are very suggestive of a Ghon complex, largely because of their subpleural situation.

SUMMARY

This paper is based on a study of twenty-three cases of hamartoma of the lung. In three of these cases, the tumor was removed surgically. In the remaining twenty cases, the tumor was discovered at necropsy. These twenty cases were part of a consecutive series of 7,972 cases in which necropsy was performed. The incidence of hamartoma of the lung in this series of 7,972 cases was 0.25 per cent. This tumor occurs more frequently than has been recognized. It is strictly benign and only occasionally causes symptoms. In most cases the diagnosis has to be made by roentgenographic examination. A hamartoma should be suspected in every case of solitary lesion of the lung. Frequently, this tumor cannot be distinguished from other lesions of the lung until a specimen of the tumor is examined microscopically. Treatment consists of excision of the tumor. One should try to conserve as much pulmonary tissue as possible.

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BRONCHIAL ADENOMA TREATED BY PULMONARY RESECTION

Case Reports

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THE rapid progress in thoracic surgery has permitted the use of pulmonary resection in the treatment of bronchial adenoma.[1, 3, 5, 6, 9, 18] Though these tumors were first treated by endobronchial removal, pulmonary resection is preferable for the following reasons: (1) It offers a definitive cure; (2) the hazards associated with the damaged lung distal to the tumor are avoided; and (3) some of these tumors are thought to be potentially malignant, and occasionally metastasize.[1, 2, 4]

Endobronchial removal has four indications: (1) Those cases which are not reasonable surgical risks; (2) those which involve the trachea; (3) those with abscess distal to the tumor which are best prepared for subsequent resection through improvement in the bronchial drainage; and (4) the rare ones in which the tumor is entirely within the bronchus, easily accessible, and attached by a long slender pedicle.

The tumors in the following ten case reports all have the same fundamental features characteristic of bronchial adenoma, and in each instance the extra bronchial portion was several times larger than the endobronchial element. The classification of these tumors as malignant[1, 2, 10, 20, 23] or benign[8, 11, 17-19, 21, 22] is the pathologist's decision.

Case 1.— case reports

History.—H. O'D., a 30-year-old married woman, had severe coughing attacks for five years, associated with expectoration, pleurisy, fever, and night sweats. A wheeze appeared in 1942. Physical examination was consistent with obstructive emphysema in the left lower lobe, and there was both a palpable and audible rhonchus. The x-ray film taken upon expiration showed mediastinal shift to the right, and several small round discrete areas near the hilum (Fig. 1*A*). In the lateral film the smaller shadows were found to lie in the apex of the left lower lobe, but one larger shadow 2 cm. in diameter remained visible at the hilum. Bronchoscopy revealed a round smooth tumor in the left lower lobe bronchus. A biopsy was easily taken from the tumor, but no neoplastic cells were found. At operation in February, 1943, the left lower lobe was removed without difficulty by

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the individual ligation technique. The pathologist's report was adenoma with cystic dilatations distal to it (Fig. 2*A*). Regional lymph nodes were positive for tumor cells. The postoperative course has remained uneventful.

Comment.—The capsule of these tumors, together with the mucous membrane, is often so thick that diagnostic cells may not be obtained at bronchoscopy even though a very generous bite is taken. This is in marked contrast to the nonencapsulated carcinomas which are easily diagnosed from biopsy material. After one or two biopsy attempts we feel that the risk from hemorrhage is out of proportion to the information gained, since not only the tumor but the irreparably damaged lung distal to it justifies removal of the lobe.

CASE 2.—

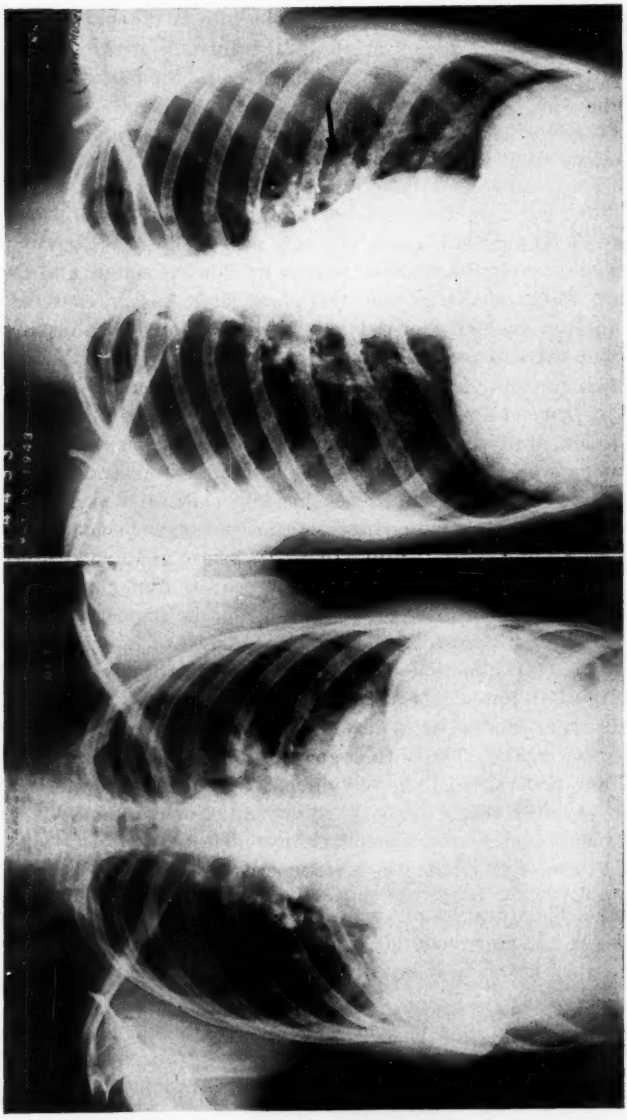
History.—A 21-year-old clerk (G. M.) was well until September, 1941, when she developed pleuritic pain, a productive cough, and fever. In October, 1941, a shadow on the chest film was interpreted as "pneumonia" in the left lower lobe. In two months resolution had occurred, but there remained a round discrete shadow near the hilum. She was well for one year before the symptoms returned. In December, 1942, a transient wheeze appeared. In March, 1943, the patient entered the Mt. McGregor Sanatorium, where at bronchoscopy a round smooth tumor was found in the left lower lobe bronchus. She was then transferred to Ray Brook for surgical therapy, at which time the main symptoms were fatigue, dyspnea, and paroxysmal coughing attacks. Physical examination revealed a transient rhonchus over the left lower chest and diminished breath sounds in the same area. Chest films revealed a round discrete shadow 3 cm. in diameter near the hilum (Fig. 1*B*). Fluoroscopy showed a slight shift of the mediastinum on expiration. (Obstruction was only partial.) At operation (June 20, 1943) the left lower lobe was removed by the individual ligation technique. Hilar nodes were also removed. Postoperative convalescence was uneventful. The pathologic report was adenoma (Fig. 2*B*), and one hilar node showed the "lymphoid tissue is almost completely replaced by typical tumor tissue." Six months after operation there was no local recurrence at bronchoscopy. The patient is well and working full time sixteen months after operation.

Comment.—The duration of symptoms in this case was less than two years and yet a lymph node already had become involved. Resection should probably never be delayed any longer than is absolutely necessary.

This is an example of a patient who was thought to have tuberculosis or tuberculous hilar adenitis until negative sputum examinations and bronchoscopy revealed the nature of the problem. The x-ray shadow of a tuberculoma may be very similar.

CASE 3.—

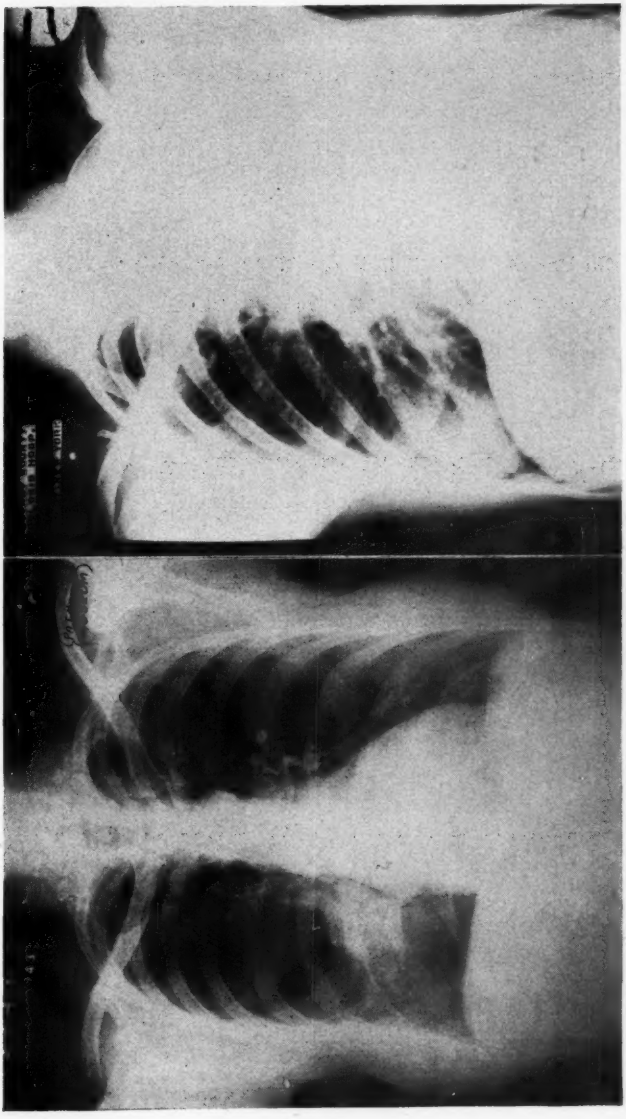
History.—L. M., a 47-year-old machine operator, had paroxysmal coughing attacks eight years before entry (to Ray Brook on July 14, 1943), associated with temperature to 103° F. Recurrent "chest colds" and a persistent cough led to a chest roentgenogram in 1943. Physical examination varied, but some examiners were able to demonstrate a



A. *B.*

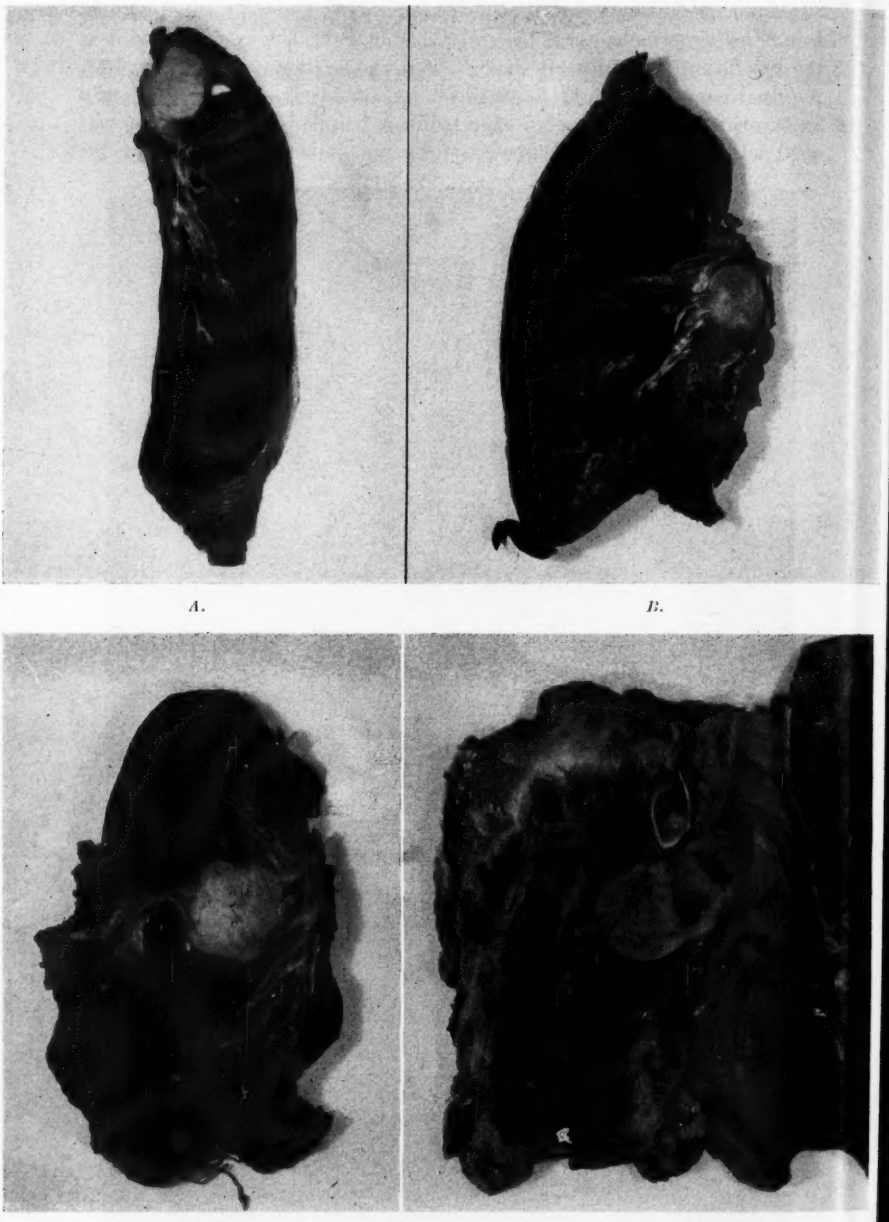
FIG. 1.—Illustrative roentgenograms of bronchial adenoma. *A* (Case 1, H. O'D.), x-ray picture taken in expiration to show tumor shadow to best advantage. *B* (Case 2, G. M.), rounded shadow not unlike a tuberculoma.

sibilant rhonchus over the right lower chest on forced expiration. Others found no abnormalities. The x-ray shadow revealed calcified nodes at the hilum and an elliptical shadow in the right lower chest (Fig. 1*C*). At fluoroscopy the right lower lobe became bright instead of cloudy on expiration and this was interpreted as entrapped air due to bronchial obstruction. At bronchoscopy (done by Dr. James Blake at Glenridge



C. *D.*

FIG. 1 *C* and *D*.—*C* (Case 3, L. M.), irregular dense shadow in lower right not unlike carcinoma. *D* (Case 4), homogenous density of left hemithorax due to secondary pleuropulmonary suppuration.

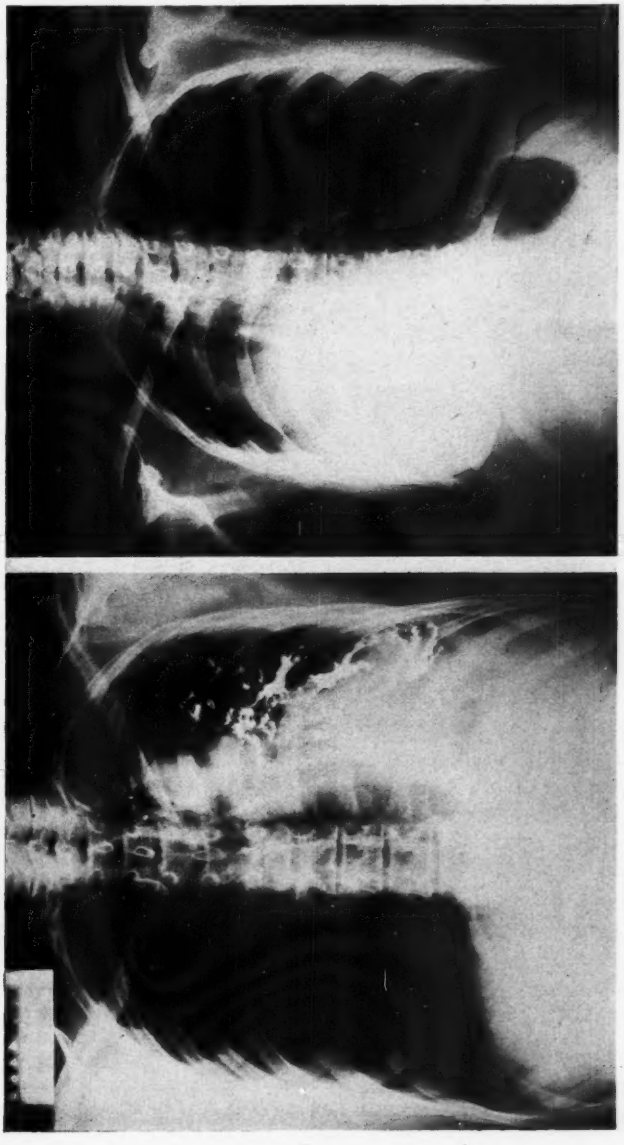


A. *B.*

C. *D.*

Fig. 2.—Photographs of specimens corresponding to those shown in Fig. 1; surgical specimens from Cases 1 (*A*), 2 (*B*), and 3 (*C*), autopsy specimen from Case 4 (*D*).

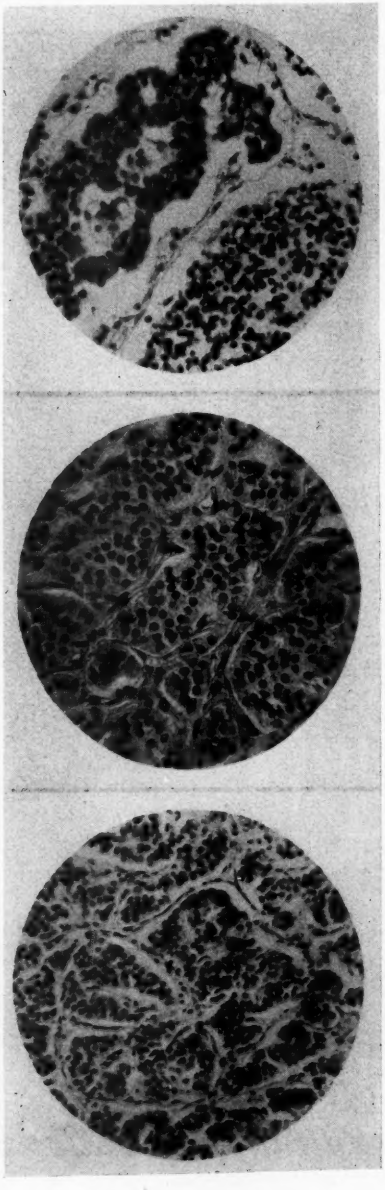
Sanatorium) a tumor was found in the right lower lobe. The biopsy material was thought to be carcinoma by one pathologist. At operation, September, 1943, no fissure could be found between the middle and lower lobes which necessitated the removal of both lobes. The pathologist's report of the surgical specimen (Fig. 2*C*) was adenoma, and neo-



A. *B.*

Fig. 3.—*A* (Case 5), Iiplodol shadow showing residual bronchiectasis in overdistended left upper lobe, also slight mediastinal hernia. *B* (Case 6), showing marked mediastinal shift and herniation following pneumonectomy which required correction by thoracoplasty.

plastic cells were also found in one of the lymph nodes removed with the specimen. The immediate postoperative course was satisfactory, but later on a small localized empyema developed which had to be drained and it contained tubercle bacilli (calcified glands in the chest roentgeno-



A. *B.* *C.*

Fig. 4.—*A* and *B*, Photomicrographs of stained slides showing typical histologic pattern of bronchial adenomas. *C*, Photomicrograph of stained slide showing metastatic lesion in lymph node, seen in five cases.

gram). Chest drainage continued for some time, but the bronchopleural fistula soon closed. The cutaneous sinus still requires a small dressing.

Comment.—The diagnosis of carcinoma may or may not have been an error, since the classification of these tumors is still a histologic dispute. However, our therapeutic attack has been based upon the belief that these tumors are "clinically benign" since as yet we are unaware of a report (1) where death was due to metastases, and (2) where the size of an involved node (either at autopsy or exploratory thoracotomy) was large enough to interfere with the mechanics of respiration.

CASE 4.—

History.—A 25-year-old woman (J. W.) entered Ray Brook on Oct. 27, 1943, with a diagnosis of chronic empyema of ten years' duration. In the years 1926, 1927, 1928, 1929, and 1931 the patient had episodes of recurrent "pneumonia." In 1933 an empyema developed and it was drained by rib resection. Drainage continued for six years but then stopped. Soon after, however, an empyema necessitatis developed and a bronchopleural fistula could be demonstrated. In 1943 the patient entered Glenridge Sanatorium and, upon suspicion of a bronchogenic tumor, was referred for bronchoscopy and surgical treatment of the empyema. On physical examination the left side of the chest was much smaller than the right; it was immobile and the breath sounds were absent. The left lung field was completely obscure in the chest roentgenogram (Fig. 1*D*). At bronchoscopy a tumor was found level with the tracheal carina and completely filling the left stem bronchus (Fig. 2*D*). A biopsy was taken, followed by generous bleeding. The patient's head was lowered and her right and only functioning lung protected by constant aspiration. In ten minutes the bleeding had stopped and upon returning to her room the patient was instructed to lie on her left side. During the rest of the day she coughed up some blood periodically, but the amounts were not alarming and her blood pressure, pulse, and respirations did not change significantly. At 2 A.M. she suddenly called her nurse, who arrived in time to find her gasping weakly for air. An emergency bronchoscopy was too late, but did reveal a large clot of blood obstructing the right stem bronchus (Fig. 2*D*). It was speculated that a clot had formed along the left tracheal wall since the patient had been instructed to lie on that side, and that during her sleep she had rolled over on her back or right side, dislodged the clot, and aspirated it into the right bronchus.

Comment.—This case points out two salient features: (1) the risk of hemorrhage especially during bronchoscopic manipulation; and (2) the extreme pulmonary destruction and ultimate result when suppuration occurs in these untreated cases.

CASE 5.—

History.—C. C. is a 34-year-old white married man whose illness began in 1934 with periodic episodes of dyspnea upon exertion. In the years 1937, 1938, 1939, and 1940 he had "pneumonia" with x-ray evidence of atelectasis of the left lower lobe. With each illness he raised large quantities of purulent sputum and had a fever, and upon entrance to the Homer Folks Hospital he reported a loss of forty pounds in weight. On several occasions he had raised small amounts of blood, and at intervals had noted a wheeze. Findings at physical examinations varied from time to time depending upon the degree of bronchial obstruction, but in the main they were consistent with suppuration and atelectasis of the left lower lobe and obstructive emphysema of the left upper lobe. Chest roentgenograms showed complete obscuration of the lower two-thirds of the left chest and many cystic-appearing ring shadows in the upper third. Bronchoscopy revealed a round smooth tumor in the left stem bronchus with its pedicle on the medial wall opposite the orifice to the left upper lobe. The tumor completely obstructed the stem bronchus on expiration, but allowed a small amount of air to enter the left upper lobe on inspiration. The most interesting bronchoscopic finding was the movement of the tumor up and down the bronchus with each respiratory effort, as though it had a pedicle. At operation (Aug. 30, 1940) the vessels to the lower lobe were ligated individually and the lower lobe bronchus opened at its carinal junction with the upper lobe bronchus. It was then possible to excise the medial wall of the stem bronchus and the dumbbell-shaped tumor. Plastic closure of the bronchus was begun slightly below the tracheal carina and carried downward to the distal wall of the upper lobe bronchus. A significant stenosis did not occur since the stem bronchus still accepts a 7-40 bronchoscope with ease. No tumor cells were found in the mediastinal nodes resected with the lobe. The postoperative course was satisfactory although a small empyema developed as a result of the accidental rupture of a large pulmonary abscess during removal of the lobe. The empyema quickly disappeared with routine drainage. Eight follow-up bronchoscopies in over four years have failed to demonstrate local recurrence. The history and microscopic slides were sent to six well-known and able pathologists for histologic diagnosis. Three classified the tumor as a carcinoma and three others thought it was an adenoma. The patient is in excellent health today and has rarely missed a full day's work in the last four years. A bronchogram reveals extensive bronchiectasis in the overdistended left upper lobe, yet the patient is essentially asymptomatic (Fig. 3*A*).

Comment.—Although the surgical specimen proved this to be a dumbbell-shaped tumor without a pedicle, its movement up and down within the bronchial tree because of bronchial peristalsis gave the operator a deceitful impression that the tumor was pedunculated. The extra-

bronchial portion was several times larger than the endobronchial element, and under no circumstances could have been totally removed by endobronchial methods.

Bronchial obstruction at the level of the left upper lobe demonstrates most of the pulmonary complications associated with these tumors. There were atelectasis and suppuration in the lower lobe, and obstructive emphysema and bronchiectasis in the upper lobe. At the present time it is unlikely that the upper lobe is contributing much to the patient's respiratory function, since for many years before operation it was valueless because of obstructive emphysema (dyspnea was an outstanding symptom), and now it is of little use because of overdistention emphysema and bronchiectasis.

CASE 6.—

History.—G. A., a 32-year-old married woman, entered the Homer Folks Hospital in September, 1942, because of repeated bouts of pulmonary suppuration. For nineteen years she had had paroxysmal attacks of coughing, but paid little attention to them until four years before entry when shortness of breath prevented all athletic activities. She entered another hospital twice in 1941 because of pulmonary suppuration, and at the last entrance bronchoscopy was done and a tumor of the right lower lobe bronchus was found. It was "completely" removed at the third bronchoscopy and the patient remained well and able to work for one year. In July, 1942, the patient returned to the hospital with another attack and at this entrance a bronchogram was done, followed by chills and fever (temperature) to 106° F. She did not improve in the hospital and elected to return home where barbiturates, narcotics, and special nurses were required in an effort to control the patient's symptoms. She was referred to the Homer Folks Hospital in September, 1942. Physical examination was consistent with the x-ray evidence of an ateletic right lower lobe and some shift of the mediastinum to the right. No wheeze was demonstrable and at fluoroscopy the mediastinum remained fixed on expiration. Bronchoscopy revealed a round smooth tumor filling the right lower lobe bronchus, and purulent material oozing upward from the suppurative process beyond it. The biopsy report was adenoma. At operation (Oct. 1, 1942) a severe pleuritis was encountered with complete obliteration of the interlobar fissures, which necessitated a pneumonectomy. Mediastinal nodes were removed with the specimen. The pathologic report noted: (1) typical bone trabeculae; and (2) the tumor permeating the capsule and infiltrating by extension to the adjacent lymph node. Where the tumor had infiltrated the lymph node, the lymphatic tissue was completely replaced by tumor. In the histologic examination of other regional nodes no tumor was demonstrable. The postoperative course was uneventful until just before discharge

when the patient began to complain of dyspnea. Fluoroscopic examination revealed a marked shift of the mediastinum to the right from the absorption of air and fluid (Fig. 3*B*). This was relieved by periodic refills of air (500 c.c.) until a one-stage eight-rib thoracoplasty could be done three months later. There was no recurrence at bronchoscopy one year after operation; she plays golf regularly and works full time at her usual occupation (office work).

Comment.—(1) A lobectomy is preferable to a pneumonectomy when it can be done to avoid a subsequent thoracoplasty which may be necessary to control the dyspnea from mediastinal shift and overdistention of the remaining lung. (2) Early operation before the obliteration of the interlobar fissures from pleurisy would have allowed a lobectomy. (3) The extrabronchial component was many times larger than the endobronchial portion and under no circumstances could it have been completely removed by the endobronchial route. (4) Although the nineteen-year history is evidence of a benign lesion, the permeation of the capsule and invasion of the lymph node are criteria suggesting malignancy. This evidence supports the belief that some of these benign lesions may become malignant.[7, 22, 23] (5) A bronchogram may precipitate a bout of suppuration and gives less information than can be obtained by bronchoscopy.

CASE 7.—

History.—G. K., a 60-year-old woman, had a chest cold five months before entry, which progressed and was finally thought to be an unresolved bronchopneumonia. The cough remained and the triangular shadow in the right lower lobe did not disappear. The patient was referred for bronchoscopy and surgical consultation to the Homer Folks Hospital in June, 1942. Physical examination revealed slight dullness and diminished breath sounds posteriorly in the cardiophrenic angle. No wheeze was demonstrable. Two bronchoscopies were done and a tumor visualized in the right lower lobe bronchus, but biopsy material failed to demonstrate neoplastic cells. Operation (June 30, 1942) was recommended because of the possibility of (1) malignancy, and (2) the irreparable damage distal to the tumor (bronchiectasis). Lymph nodes were removed with the right lower lobe. The pathologic report was adenoma and in one area osteoid tissue was disclosed. The lymph node was free from pathologic lesions, but extensive bronchiectasis was present distal to the tumor. Her postoperative course was very satisfactory and bronchoscopy one year later showed no recurrence locally. She remains asymptomatic to date.

Comment.—Since cancer occurs most frequently in the fifth and sixth decades, this patient's age was an indication rather than a contraindication to pulmonary resection.

CASE 8.—

History.—M. G., a 23-year-old achondroplastic woman, had a persistent cough productive of small amounts of blood, in the years 1933 and 1937. A chest cold and a severe intractable cough led to x-ray examination in 1939, which revealed a triangular shadow in the cardiophrenic angle. In 1941 she expectorated one teaspoonful of blood on two occasions and entered the Homer Folks Hospital for diagnostic studies in September of the same year. Physical examination was essentially negative in so far as the chest was concerned. A wheeze was not demonstrable. Two bronchoscopies revealed a tumor far down in the right lower lobe, but biopsy material did not disclose neoplastic cells. The patient did not accept the surgical recommendation until November, when she had a rather severe hemorrhage. At operation (Dec. 10, 1941) a partially atelectatic right lower lobe was removed and an uneventful convalescence followed. The pathologic report noted: (1) markedly dilated capillaries giving the tumor a hemangiomatous structure, and (2) the capsule in many areas infiltrated by the tumor, apparently spreading in the lymph and blood spaces. As a great number of sections were made, in a series of eight sections a small tumor nodule was found on microscopic examination a small distance away from the capsule in the lung parenchyma. In other areas clusters of tumor cells were seen in the lumen of the alveoli. One parabronchial node was negative. The patient's postoperative course was satisfactory and three bronchoscopies, to April, 1944, showed no local recurrence. She is working full time at her former occupation (office work).

Comment.—The eight-year preoperative history and the course since operation (three years) suggested a benign lesion, yet there was little doubt in the pathologist's mind but that this tumor was potentially malignant.

The failure to demonstrate a wheeze in these cases was due to the fact that the lung distal to the tumor was not exchanging air.

CASE 9.—

History.—P. B. is a 58-year-old laborer whose illness began in 1932. He had several attacks of "pneumonia" and developed an empyema in 1934 which was drained without complications. For some time he was thought to have tuberculosis because of repeated hemoptyses. Later, bronchoscopic examination revealed a tumor in the right lower bronchus, a biopsy of which led to the diagnosis of adenoma. The tumor was incompletely removed by several attempts through the bronchoscope, and the patient was then sent to Dr. James Blake, who sent him to Ray Brook for surgical therapy, March 6, 1941. Physical examination revealed evidence of an old empyema and a functionless lung in the lower half of the right side of the chest. The patient's general condition was good. Chest x-ray films showed a uniform

density throughout the right lower lung field. At operation there was an obliteration of the pleural space, but the lower lobe could be defined in all its surfaces except medially, where no line of cleavage could be developed between the pericardium and the orange-sized tumor. Blind dissection was thought hazardous and resection was considered possible only by including the pericardium. This did not seem justifiable in a 58-year-old man who had already lived seven years with a tumor that was "benign." Postoperative convalescence was uneventful and the patient is still living more than three years after operation, though the symptoms are still present.

Comment.—These patients are frequently found in tuberculosis sanatoriums because of the recurrent hemoptyses. This is the only inoperable case we have found in our entire series of lobectomies for benign lesions (bronchiectasis, cysts, adenomas, tuberculosis).

CASE 10.—

History.—A. A., a 43-year-old married woman, entered the Homer Folks Hospital August, 1939, because of extreme dyspnea and noisy breathing. In 1930, nine years before this entry, the patient noticed for the first time a definite substernal rattle during ordinary breathing. She suspected a foreign body, since at the same time she had had some teeth extracted. A foreign body was never found, but in 1934 bronchoscopy was done elsewhere and a tumor was found occluding the left main bronchus. At a second bronchoscopy one week later it was noticed that it actually encroached upon the distal end of the trachea at its junction with the bronchus. Dr. Konzelmann's pathologic diagnosis was adenocarcinoma, grade 2. At intervals during the next four years the patient had many bronchoscopies and pieces of tumor were removed by electrocoagulation. Her condition was improved and the atelectatic left lower lobe re-expanded at one time. Several courses of roentgen therapy were also given. Wheezing, mild hemoptyses, and increasing dyspnea were the outstanding symptoms during the years of palliative therapy. On physical examination one was struck by her extremely healthy appearance. She was well nourished, in good spirits, and complained only of dyspnea. X-ray films revealed atelectasis of the left lung and marked shift of the trachea and mediastinal structures into the left side of the chest, with extreme overdistention of the right lung. At bronchoscopy the papillomatous neoplastic tissue had extended 3 to 4 cm. up the trachea and also had spread across the tracheal carina to involve the right stem bronchus, which was one-third its normal diameter. A biopsy was taken and the patient allowed to sit up. She quickly showed signs of air hunger and expired in a state of asphyxia. Before death, however, the bronchoscope was quickly reinserted but the right stem bronchus could not be found. It was noted at necropsy that one of the papillomatous tumor masses hanging from the wall of the trachea apparently had been inhaled into the right stem bronchus

resulting in complete obstruction. A small metastatic nodule was found in the near-by lung parenchyma, but no other metastases were present in the body.

Comment.—This was a very puzzling case. The history of bronchial obstruction was more than nine years in duration, and at this entry, except for respiratory distress, the patient was in excellent general

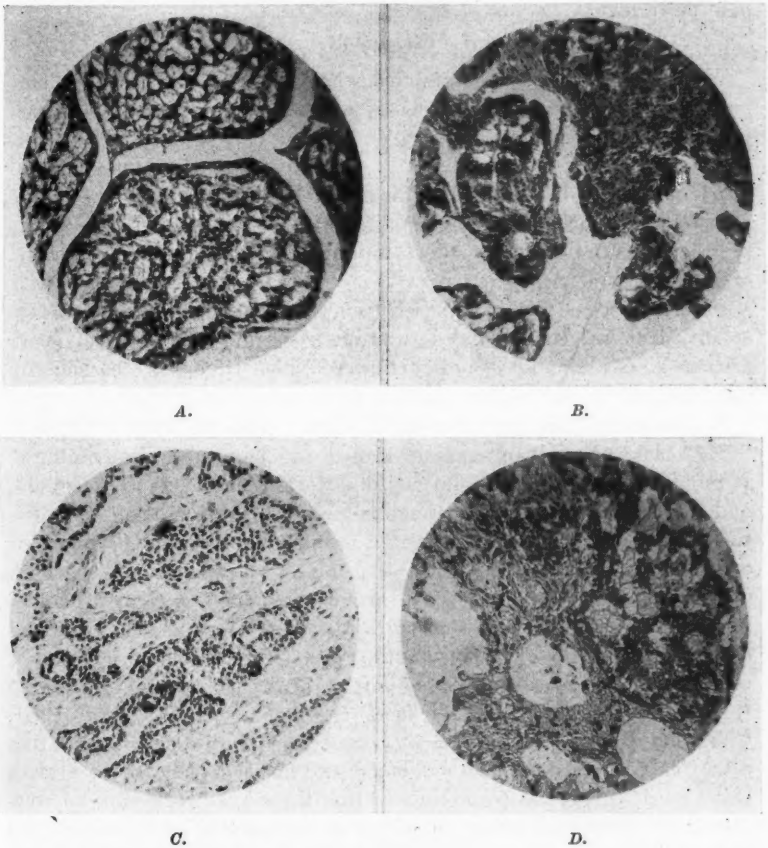


Fig. 5.—Photomicrographs of stained slides from Case 10. From 1934 bronchoscopic biopsy: *A*, showing typical adenomatous pattern; *B*, showing carcinomatous pattern. (Courtesy C. L. Jackson.) From autopsy material in 1939: *C*, showing predominantly carcinomatous pattern of bronchial tumor; *D*, showing the same type of lesion in a metastatic nodule within the lung.

condition. She died of an accidental asphyxia. Microscopic examination of a biopsy specimen in 1934 showed a definite adenomatous pattern (Fig. 5*A*) except in one area in which there was an irregular growth of cells suggestive of malignancy (Fig. 5*B*). Examination of specimens taken from autopsy material five years later showed a

marked histologic transition, since the pattern was predominately malignant (Fig. 5*C*), especially the metastatic nodule found in the near-by lung (Fig. 5*D*). No other metastases were found in the body. This case may be similar to those reported by Clerf and Bucher,[7] and Womack and Graham,[23] in which there was a gradual transition from a histologically benign lesion to one that was definitely malignant. The earliest histologic evidence in this case contained both benign and malignant patterns.

DISCUSSION

We have performed lobectomies whenever location of the tumor permitted because: (1) submucosal extension is not usually characteristic of these tumors, and if a pneumonectomy is done it adds but 2 to 3 cm. more of the bronchus; (2) the palpable or visible mediastinal nodes may still be resected, which is the most frequent metastatic channel; (3) morbidity and mortality rates are lower; (4) less lung is sacrificed; and (5) a subsequent thoracoplasty may be avoided (Fig. 3*B*).

Pulmonary resection completely removes the tumor and the irreparably damaged lung distal to the obstruction. At operation mediastinal glands should also be removed since they are occasionally involved.

Endobronchial therapy, though favorably reported upon,[7, 12, 13-15, 17, 19, 21, 24] lacks the advantages mentioned and has some disadvantages. It requires repeated manipulations since local recurrences are frequent, and the risk of severe hemorrhage is always a consideration. Cicatrization may occur following repeated bronchoscopic treatments with or without the use of radon. Such scarring and stenosis interferes with the cleansing mechanism of the bronchus (ciliary action, bronchial peristalsis), and predisposes to pulmonary suppuration. The principal therapeutic objective of maintaining a patent airway is defeated if cicatricial stenosis is substituted for an obstructing tumor. Even in the absence of scarring and local recurrence stenosis may occur. Clerf and Bucher[7] have noted in cases treated by bronchoscopy "that after years of freedom from symptoms and no recurrence of the growth endobronchially, it has been observed that there was progressive narrowing of the bronchial lumen by either an intramural or extrabronchial growth."

It is of interest that the cause of death in these cases is due, usually, to pleural and pulmonary suppuration, secondary to the bronchial obstruction, and occasionally to fatal hemoptyses following bronchoscopic manipulation,[8, 22] yet there is no record of a death due to metastases.[8]

SUMMARY

Ten cases of bronchial adenoma were reported. Six patients had lobectomies, one had a pneumonectomy, and one had an exploratory

thoracotomy; two patients died following bronchoscopy. The response to pulmonary resection was very favorable and there were no deaths. In five cases lymph node involvement was encountered.

The reasons were presented for pulmonary resection, especially lobectomy with the removal of regional lymph nodes.

The authors are grateful to all those who contributed to the diagnosis, preoperative preparation, and postoperative care of these patients and especially for the technical assistance of Mr. Joseph Kurung.

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A NEW GUIDE IN THE OPERATION FOR ESOPHAGEAL HIATUS HERNIA OF THE DIAPHRAGM

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THE surgical treatment of esophageal hiatus hernia, though similar in principle to that of hernia elsewhere, has not been generally adopted, even by surgeons who have successfully invaded the mediastinum for more formidable purposes. From the histories of patients with this deformity, we have learned that many continue to suffer for years even when following a careful dietary regimen. Symptoms persist in spite of medical treatment and if operation is mentioned, it is merely to exclude it. One reason is that the operation for the cure of hiatus hernia involves a procedure generally considered as extensive intervention with a higher mortality than herniorrhaphy applied for the cure of rupture in other parts of the abdominal cavity. For other forms of hernia, operative procedures have been well established. But for esophageal hiatus hernia, the method of approach and the technique of dealing with the sac and the hiatus are still in the controversial stage. Any simplification of method to aid in understanding this surgical problem is relevant.

We have used both methods of approach, abdominal and thoracic. Much has been written in favor of and in opposition to each. Harrington[1] of the Mayo Clinic has reported 102 cases of esophageal hiatus hernia, all of which were repaired through an abdominal incision. While there has been no general surge to follow this method, he has pointed out its advantages. In this report he has given an excellent description of the anatomy of the central area of the diaphragm as seen from below. Among the advantages afforded by the abdominal approach he mentions the opportunity for direct open examination of all structures in the upper abdomen for lesions which might be the real cause of the patient's complaints. This is of no minor importance when one takes into account the fact that peptic ulcer, cholecystitis, gallstones, early cancer of the stomach, subacute or chronic pancreatitis, and aortic aneurysm may be confused symptomatically with hiatus hernia. Then, too, it is common knowledge that hiatus hernia often exists without causing symptoms.

It is our practice to operate for hiatus hernia after it has been demonstrated by the roentgen ray, and after all other conditions with symptoms simulating those of this deformity have been ruled out, as completely as modern methods of diagnosis permit.

In my series of fifty cases of esophageal hiatus hernia, the thoracic route was employed in twenty-six, and the abdominal approach

Read (by title) at the Twenty-Fifth Annual Meeting of the American Association for Thoracic Surgery, Chicago, Ill., May 5 and 6, 1944.

in twenty-four. Having experienced more difficulties and failures from the abdominal approach, I have adopted the thoracic route because it offers better exposure and a definite anatomic landmark for locating the hernial sac.

There were four deaths in this series of fifty patients, a mortality of 8 per cent. There were three deaths (12.5 per cent) in twenty-four operations carried out through the abdominal approach and one death (3.85 per cent) among twenty-six patients operated upon by the thoracic route. Two patients died from mediastinitis following injury to the esophagus. One other patient died twenty-six days after operation from a cerebral accident, and a fourth patient died of peritonitis due to perforation from a silk suture used to anchor the cardia to the diaphragm.

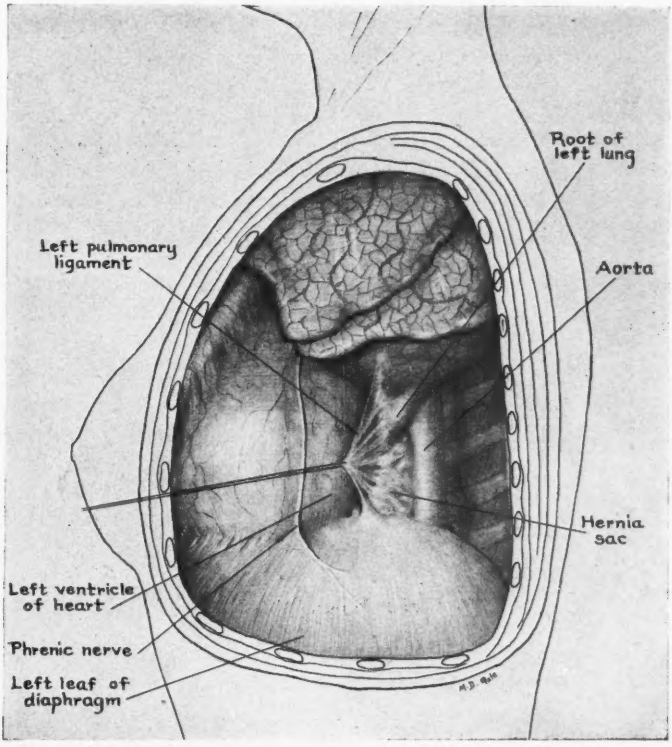

Fig. 1.—Pleura and left pulmonary ligament covering the hernial sac.

Three of these deaths were avoidable. Injury to the esophagus is a distinct liability and accounted for two of the four deaths. Before handling any tissues in this region, the operator should have an accurate knowledge of the location of the hernial sac. Prolonged search for the sac in the presence of continuous motion of the heart, lung, and

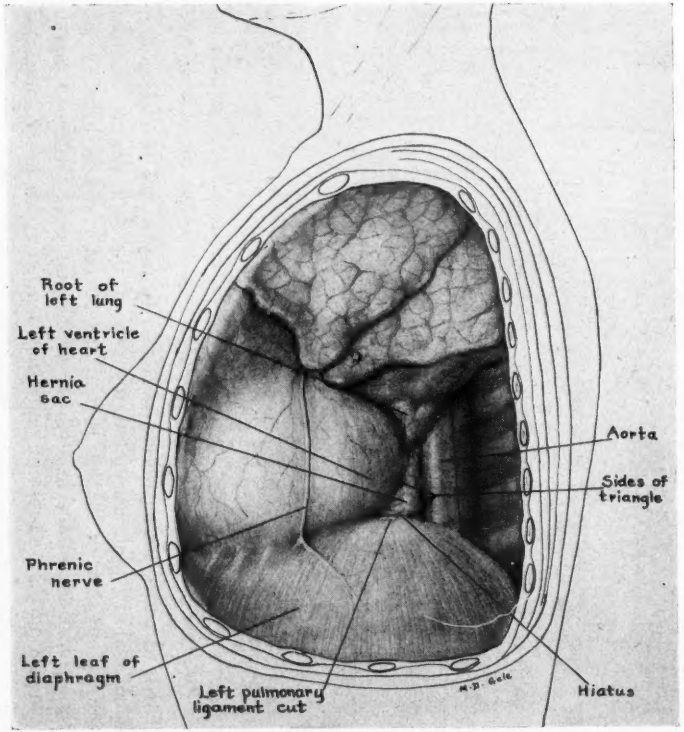

Fig. 2.—Structures bounding the triangular space above the hiatus.

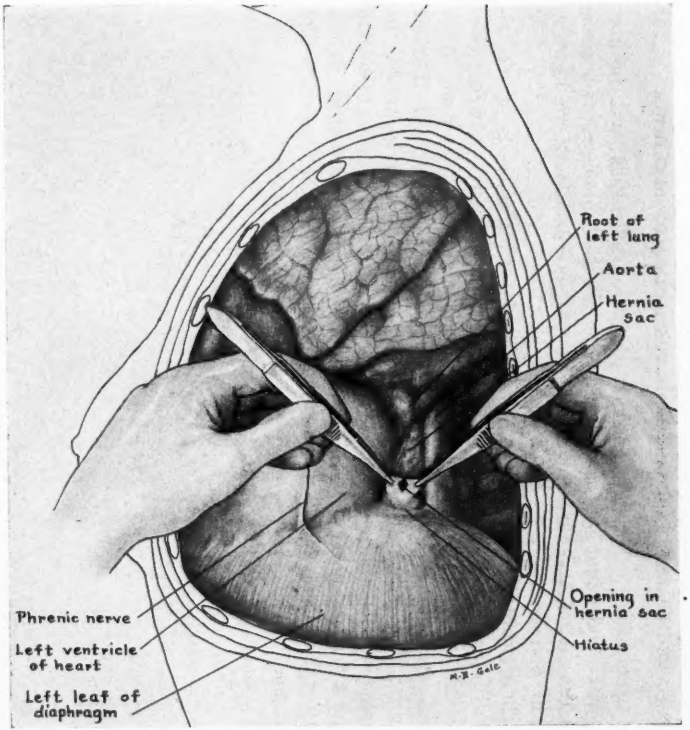

Fig. 3.—Incising the pleura and peritoneum composing the hernial sac.

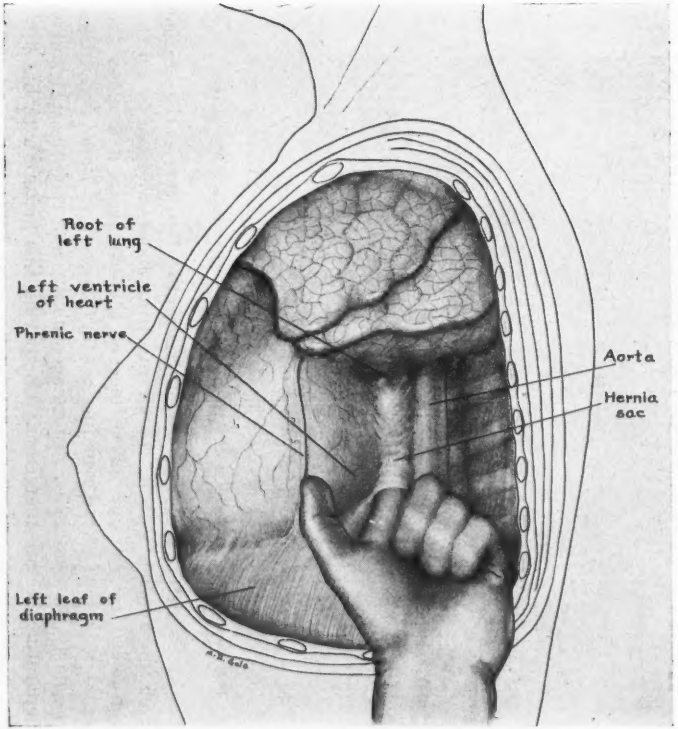

Fig. 4.—Inserting the forefinger to show the full length of the sac.

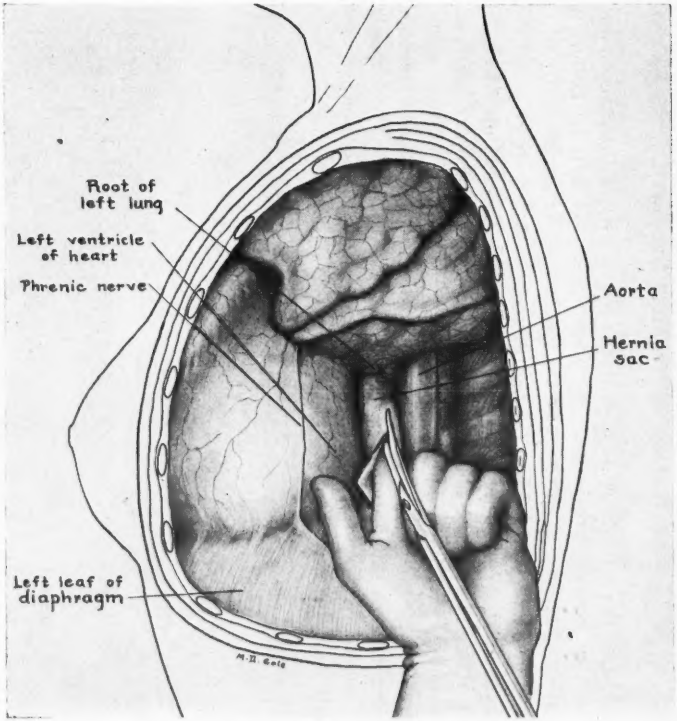

Fig. 5.—Splitting the sac.

diaphragm has a tendency to disturb the equanimity of the surgeon and discourage orderly procedure. We found also that it is hazardous to suture the stomach to any part of the innervated diaphragm.

We have had no deaths in the last nineteen cases, in six of which the abdominal route was used, and in thirteen the thoracic approach. I have found that in the abdominal exposure the field of operation is inaccessible, often inordinately so, by the high position of the central portion of the diaphragm and the roofing of the rib cage and sternum. To overcome this handicap, long instruments are required. For example, our scissors are eleven inches long, depressors fourteen inches, and needle holders ten inches.

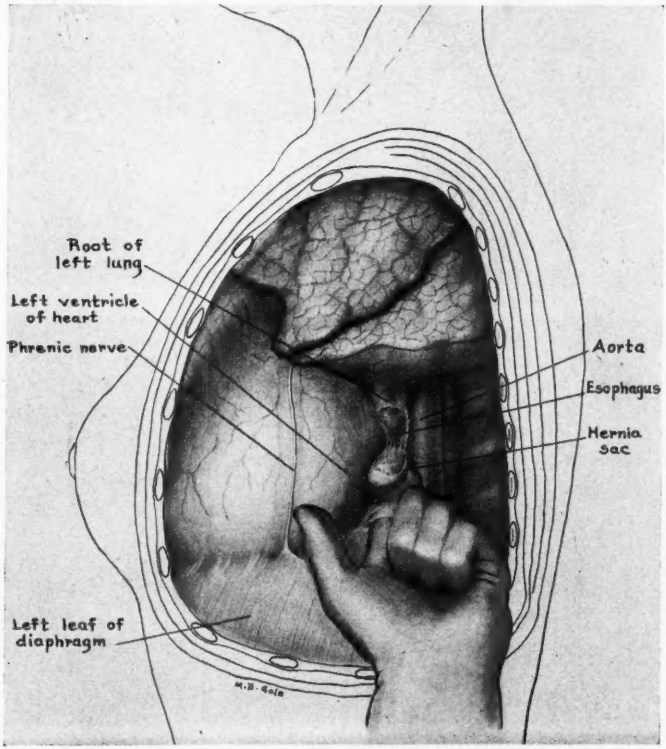

Fig. 6.—Freeing the sac from attachments to the esophagus and aorta.

The sac, which extends into the mediastinum, often carries the cardiac end of the stomach with it. Observing from above, we have found the sac attached to the anterior surface of the esophagus and along the internal aspect of the descending aorta. Therefore, these structures, particularly the esophagus, require accessibility and the utmost deftness in separating the sac therefrom. Comparing this picture with the situ-

ation encountered in locating and extirpating the sac through an abdominal incision offers persuasive evidence in favor of thoracotomy.

In one of our patients who chanced to be considerably underweight, I obtained an excellent exposure of the hernia by a thoracic approach. Incidentally I observed a triangular space bounded on the right side by the left ventricle of the heart, on the left side by the descending aorta, and its base formed by the diaphragm. The apex reached the hilus of the lung. Within this triangular space were seen small lobules which proved to be preperitoneal fat. Separating the fat, we came upon the serosa. When this was incised through the pleura, it proved to be the peritoneum lining the hernial sac.

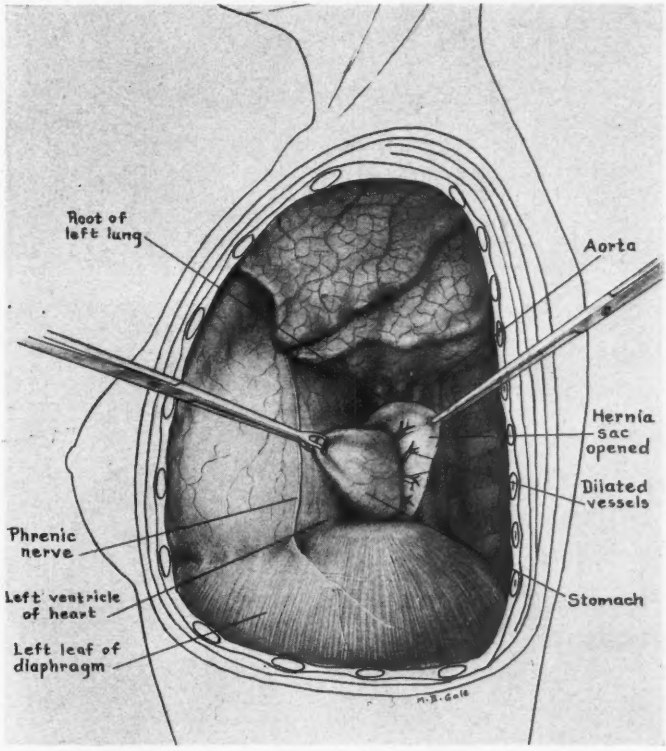

Fig. 7.—Vessels attaching the mesentery of the stomach to the peritoneal lining of the sac.

In nine cases we have corroborated this original observation. Thus we have noted an anatomic clue which greatly simplifies the identification of the hernial sac for reduction and repair of the hernia. With the body of the patient turned 45 degrees to the right, this triangle can be clearly discerned. So far as we can learn, this space has not been

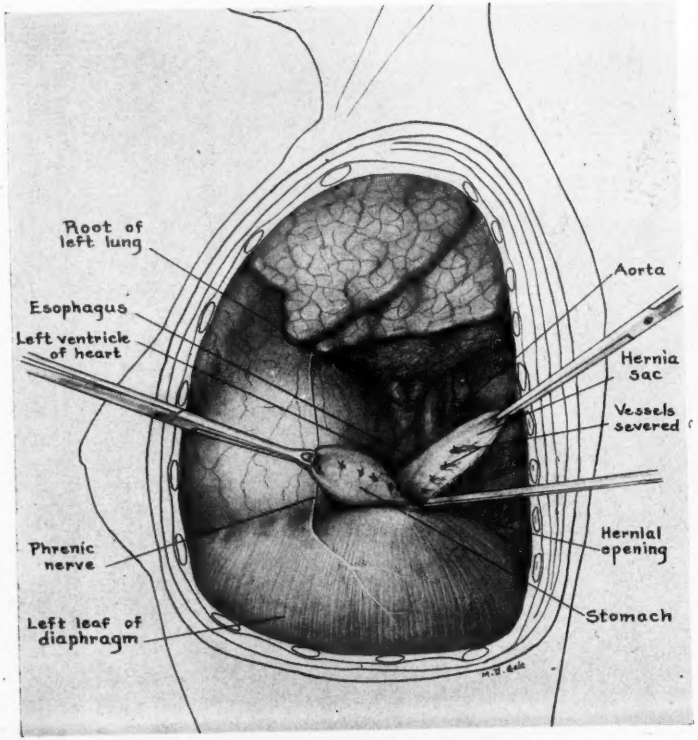

Fig. 8.—Stomach entirely free for reduction.

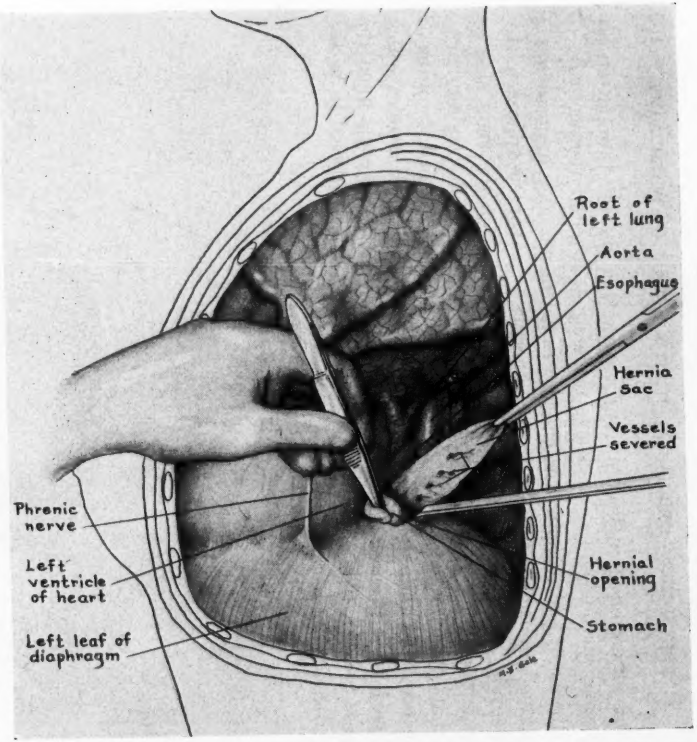

Fig. 9.—Reduction of the cardia to its normal position below the diaphragm.

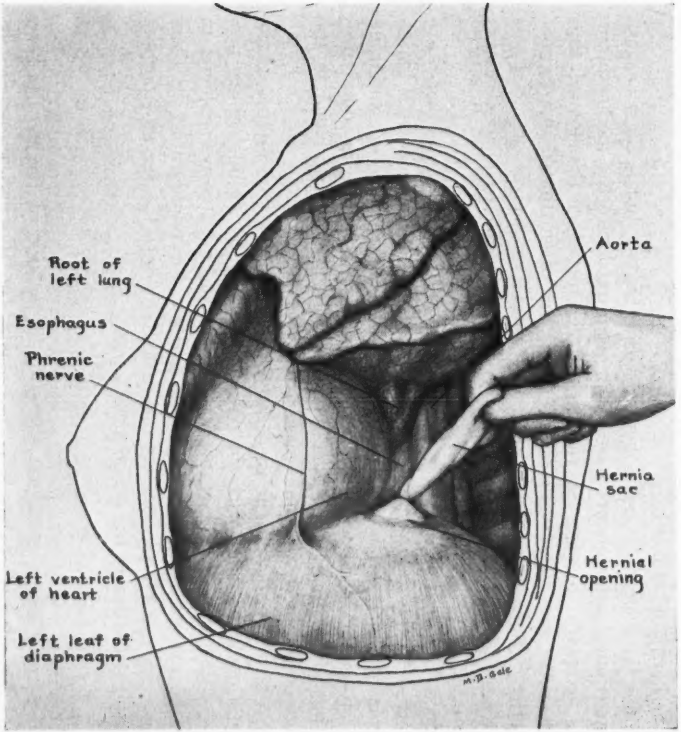

Fig. 10.—Ligation at the point of severance of the hernial sac.

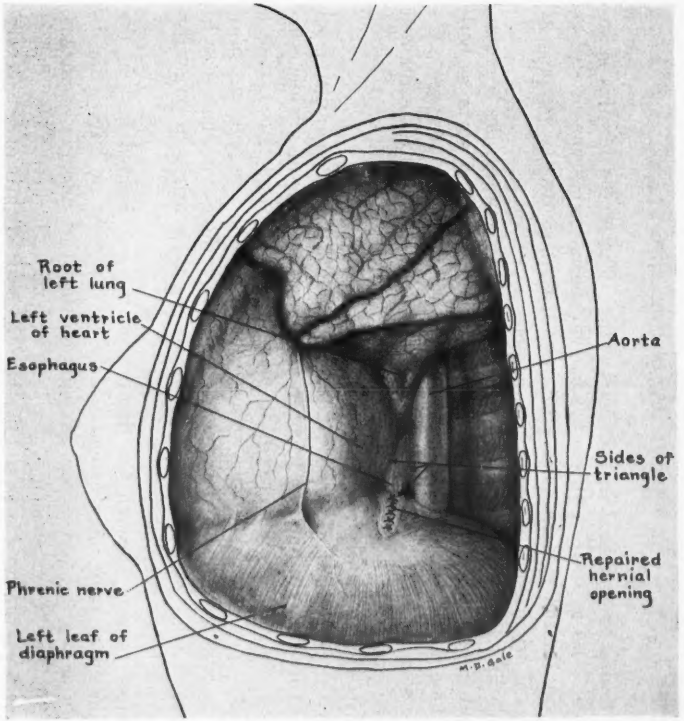

Fig. 11.—Interrupted sutures repairing the hiatus.

mentioned or described in anatomic works. The reason for this is apparent. Its existence hitherto has had no special significance except as a space in the mediastinum. But now that it serves the purpose of surgical orientation, its recognition becomes important.

We find that the hernial sac invariably passes upward, lies superimposed upon the esophagus, and overlaps the descending aorta as both of these structures pass through the floor of this triangular space. We have also discovered why the cardia of the stomach is so often contained in the sac. Herniation of the serosa to form the sac carries the cardia and its vessels with it.

When we consider the great depth of this field of operation from the thoracic wall, and the number of important structures which surround the triangle described, it may be readily understood that a variety of obscure symptoms arises from changes in size and tension of the hernial sac. Thus, it becomes obvious how these symptoms may be mistaken for those of other affections having their origin in structures above or below the diaphragm.

After passing through the diaphragm, the sac, located first in the mediastinum only, may extend widely to the right or left or lie directly across the mid-thorax, pressing on the heart and the esophagus, and limiting the expansion of one lung or both. The hernia may deflect or compress the esophagus and displace the heart slightly or extensively, depending upon the amount of gaseous distention in the upper chamber of the herniated stomach.

Since the stomach is not adherent within the sac, but is there because its peritoneal attachments have taken it upward into the mediastinum, it is necessary to sever the vessels in order to reduce the stomach and remove the sac. The veins at the cardia are often dilated due to constriction. Such varicosities probably explain the source of blood loss and anemia so common in patients suffering from esophageal hiatus hernia.

Bock, Dulin, and Brooke,[2] and Jankelson and Morein[3] and others have referred to the discovery of blood in the stools associated with hiatus hernia of the stomach, and have stressed the importance of examining the stools for blood whenever a portion of the stomach is found projecting above the diaphragm. We have observed occult blood in the stools in 34 per cent of our cases.

We have found that the roentgenogram, to give a true picture of the hernia, must be made with the patient lying in the Trendelenburg posture. Marks[4] was among the first, if not the first, roentgenologist to use the exaggerated Trendelenburg position for photography in these cases. In this plane more bismuth gravitates into the sac and permits a better definition of the entire hernia.

OPERATIVE PROCEDURE

The fact that an anatomic guide to the location of the sac has been definitely established has led us to favor the thoracic approach. In

opening the thorax, the incision is made over the seventh rib from its sternal attachment to a point posteriorly beyond the tubercle. A subperiosteal resection of the rib is then made. The pleura is incised and the receding left lung protected with a warm, moist gauze pad. Any adhesions of the hernial sac to the diaphragm, the lung, the pericardium, the esophagus, or the aorta are severed.

The triangle described in this paper is then identified. We often find the left pulmonary ligament overlying a portion of its base and left border, as in Fig. 1. This is cut just above its attachment to the diaphragm, thus providing a full view of the triangle in which is found the hernial sac (Fig. 2). The base of the triangle is formed by the diaphragm, the right side by the border of the left ventricle of the heart, and the left side by the descending aorta. The apex of this triangle reaches the root of the lung. After brushing off the preperitoneal fat, the sac is picked up and incised (Fig. 3). Through this opening, a finger is inserted (Fig. 4). The sac is likely to be larger than was assumed from the roentgenogram. It may contain stomach, colon, omentum, or small intestine. It is covered with a very thin serosa, the pleura, on the outside and is lined with peritoneum. To the peritoneum within the sac, the stomach with its vessels is often attached by a short mesentery.

Placing the index finger of the left hand in the sac, we can determine the space it occupies in the mediastinum (Fig. 5). By sponge dissection all adhesions to esophagus, lung, and aorta are separated (Fig. 6). In Fig. 7 we note the row of vessels attaching the stomach to the peritoneum lining the sac. These vessels are ligated and severed (Fig. 8). The stomach is then reduced (Fig. 9). The hernial sac is finally cleared of its attachments and removed (Fig. 10). The base of the sac may be found broad, and instead of ligation it must be closed by interrupted sutures of fine silk. Reinforcement of the hernial orifice is accomplished by the use of interrupted sutures of medium-sized silk, drawing the membranous portion of the diaphragm into close relation with the esophagus (Fig. 11).

With this step completed, the aperture in the chest wall is closed with running sutures of fine chromic catgut in the pleura and muscular layers. This line of union is reinforced by interrupted mass sutures of nylon.

Before these steps in the operation are undertaken, there arises the question of securing a quiet field in which to operate. Heretofore, this has been obtained by exeresis, cutting or crushing the phrenic nerve, or injecting it with alcohol or novocain. In no case have we excised or severed the phrenic nerve, but we have employed the other three methods of local anesthesia to secure temporary paralysis of the diaphragm. From our observation during the postoperative period, we have found that patients in whom the nerve was crushed manifested a prolonged degree of dyspnea. It was necessary to keep one patient in the oxygen

tent for a period of four days. By crushing the left phrenic nerve, the left lung met with such sudden interruption of activity that, in spite of positive pressure anesthesia, its expansion was impeded so that almost the entire burden of oxygenation of the blood was thrown upon the right lung.

We have found it expedient to employ a local anesthetic to produce a quiet diaphragm only along enough for its repair to be accomplished. When the pleura is incised, the lung undergoes a degree of collapse which, in most instances, admits adequate approach to the hiatus. Therefore, the mildest possible anesthesia of the phrenic nerve is advisable, and no anesthesia of the nerve is preferable. In our last few cases, no anesthetic was used to secure temporary restriction of motion of the diaphragm.

If the operation is conducted on these principles, we believe that the mortality will be negligible and the procedure can be carried out by any surgeon who is familiar with operating in the thoracic cavity. It is hoped that the anatomic clue revealed in this paper will make the operation for the cure of esophageal hiatus hernia less formidable and more successful.

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A THORACOPLASTY BINDER

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DETROIT, MICH.

SOME type of brace or binder is generally used following thoracoplasty for the following three reasons: (1) it increases the amount of collapse of the chest wall, (2) it maintains this compression until rib regeneration makes the collapse permanent, and (3) it decreases paradoxical respiration. Several such braces and binders have been used at the Herman Kiefer Hospital over a period of years, but the binder to be described has superseded all of these. Its advantages are: it is reasonable in cost; the materials are easily obtainable; it is fairly comfortable; it never becomes lost or broken; and it always fits, as it is tailored to suit each individual's chest every week (for the size and shape of the chest change after each stage of thoracoplasty).

This binder has proved itself over a period of eight or ten years at this hospital, during which time it has been used on many hundreds of thoracoplasty patients. We feel that it has been of help in keeping our revision operations at a minimum. The binder is the result of various suggestions made by Major William M. Tuttle, Lt. J. Claude Day, Dr. Koert Koster, and myself.

The materials necessary are (Fig. 1):

(a) Soft sponge rubber balls in two sizes, three and four inches in diameter. These can still be obtained from the manufacturers;* if not, a satisfactory substitute can be made by folding an abdominal pad twice, to form a square four inches long on a side.

(b) Three-inch adhesive tape (nonelastic), in lengths slightly longer than the circumference of the patient's chest.

(c) Oblongs of flannelette, ten by forty inches in size, which are folded twice the long way, resulting in ten-inch squares of four thicknesses.

(d) Stockinet in two sizes, eight- and ten-inch width, which is cut into sections twelve inches long.

(e) Paper "wipes," or Kleenex, or tissue paper.

TECHNIQUE OF APPLYING THE BINDER

To have the binder applied, the patient sits straight up in bed, facing the foot of the bed, with hands resting on top of the head (Fig. 2).

From the Herman Kiefer Hospital.
Received for publication July 25, 1944.

*The plain white flannelette or Canton flannel can be obtained from any wholesale or retail dry goods merchant. The stockinet can be obtained from any surgical supply house. The three- and four-inch sponge rubber balls can be obtained from a rubber goods manufacturer, such as the Schaeffer Rubber Company or United States Rubber Company. Some of these companies are now making these balls out of synthetic or reclaimed rubber. It is still possible to obtain some of the natural rubber balls (pre-war) from some of the five-and-ten-cent stores.

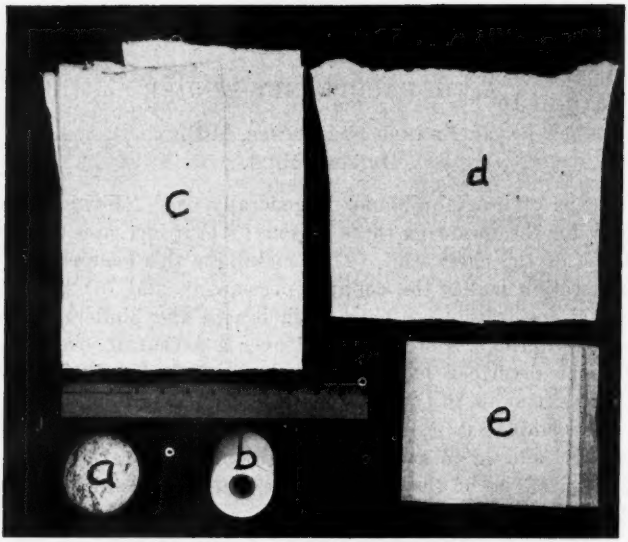

Fig. 1.—Materials for making the binder: (*a*) sponge rubber ball, (*b*) three-inch adhesive tape, (*c*) flannelette, (*d*) stockinet, and (*e*) tissue paper squares.

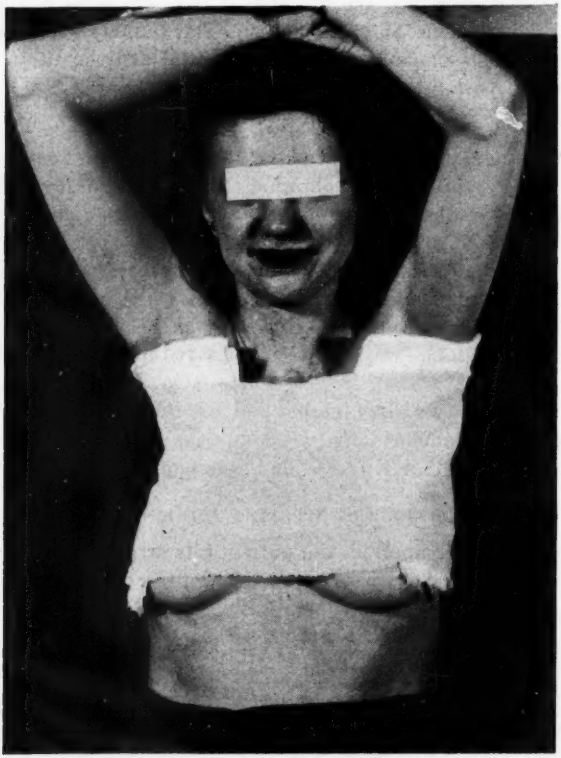

Fig. 2.—Flannelette squares and stockinet are in place.

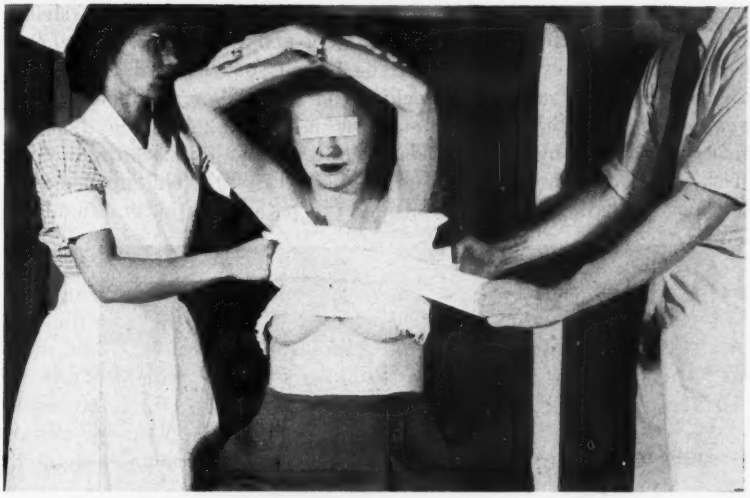

Fig. 3.—The first adhesive tape strip is being applied.

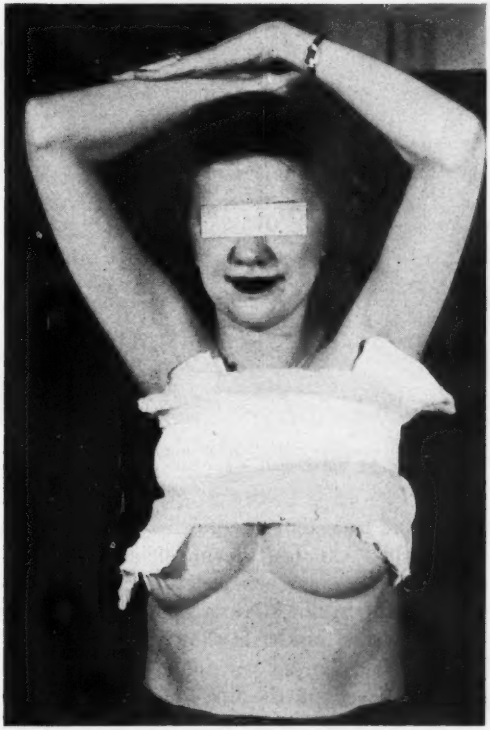

Fig. 4.—Finished binder; the flannelette protruding at the top is simply folded over the tape below it.

The nurse stands on the side of the thoracoplasty, and the physician is on the opposite side. The stockinet is placed over the patient's head down onto the chest, and one of the folded squares of flannelette is inserted smoothly under the stockinet on each side. A rubber ball is wrapped in two or three layers of tissue paper and held in the thoracoplasty depression by the physician, while the nurse places the middle of the first adhesive tape strip on the ball (Fig. 3). The nurse places one arm around the patient, pulling the patient's opposite shoulder

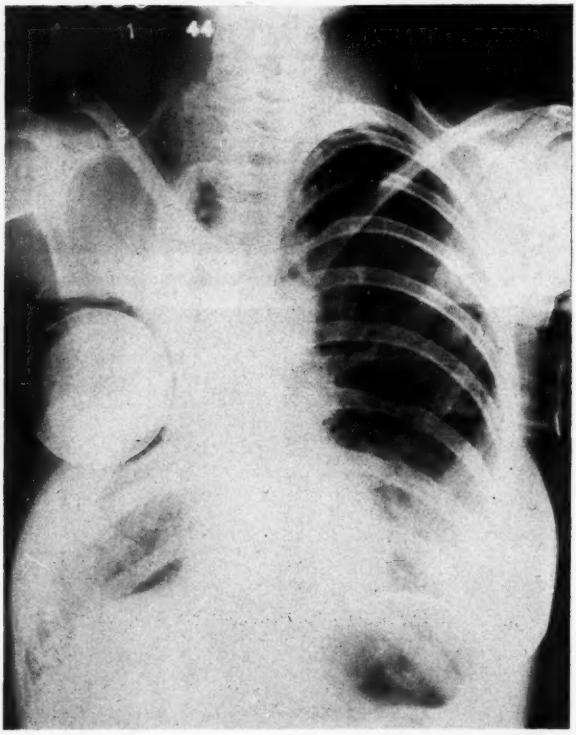

Fig. 5.—X-ray picture of patient with binder applied. Note absence of "tenting out" effect usually produced by unresected lower ribs; a contralateral pneumothorax is present in this patient.

toward her at the same time that she pushes with her fist on the rubber ball. As the patient exhales, the physician tightly smoothes the tape in place. This process is then repeated as two more tapes are applied in the same manner, one slightly above and one slightly below the first tape. The finished binder is shown in Fig. 4; the flannelette protruding at the top is then simply folded over the tape below it. The patient may bite tissues in the lips during the application of the binder to discourage coughing or talking, but this was omitted from the photograph in the interest of clarity. Fig. 5 shows the manner in

which the binder prevents any "tenting out" effect by the lower unresected ribs. Theoretically there is also pressure on the opposite lung, but in actual practice we have never noticed any ill effects from hundreds of these binders. After the first two or three binders the patient feels much better with the binder on than with it off. The binder should be applied tightly, but too tight a binder will cause a small pressure sore, and on one or two occasions, on a left-sided thoracoplasty, it has caused momentary syncope, which was easily relieved by slightly loosening the binder.

In order to save time, the nurse puts the necessary supplies at each patient's bedside beforehand, and tears off three pieces of the adhesive tape onto the foot of the bed. It is then possible to apply twenty or thirty binders in one or two hours. All the binders are cut off the same day each week, saving only the balls and the flannelette. The latter is laundered; the balls and flannelette may be used repeatedly. The patients are given baths, and then the binders are re-applied the next day. In general, a binder is applied ten days after the second and succeeding stages of thoracoplasty, and is then kept on between operations and afterward until the chest wall is firmly rebridged, which is usually about three months after the last stage. The small ball is used on most women; the large ball is used on the larger men after the third stage. Necessary x-rays are timed so that they are taken when the binder is off.

While wearing binders, the patient lies alternately on a sandbag and a rolled-up pillow for four to six hours a day in the Bisgard position to prevent scoliosis; the rubber ball is placed either directly on, or just cephalad to, the sandbag or pillow. Codeine and aspirin compound are given for discomfort as needed, and a mild hypnotic is ordered for the first two nights after each binder is applied.

THE USE OF WHOLE BLOOD TRANSFUSION IN RESECTIONS OF THE LUNG

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RECENT reports have cautioned against the use of massive blood transfusions in patients subjected to radical surgical procedures. In the case of thoracic surgery the dangers of large blood transfusions are said to be of two types.

1. Experiments on dogs conclusively prove that sodium citrate causes fatal toxic reactions under certain conditions.[1, 2, 3] In order to cause a fatality 0.25 to 0.30 Gm. of sodium citrate per kilogram must be given in less than fifteen minutes. If the time of administration is prolonged or if calcium ions are supplied death does not occur.[3] (As ordinarily preserved, a pint of blood contains 2.5 Gm. of sodium citrate. If this blood is given to a 50 kilogram man in fifteen minutes the dose of citrate would be only 0.05 Gm. per kilogram. It would be necessary, therefore, to inject five times that amount of blood [2,500 c.c. in fifteen minutes] to approach the fatal dose of sodium citrate in animals [0.25 Gm. of citrate per kilogram in fifteen minutes or less].) As we have previously stated,[4] this rate of transfusion is not easily obtainable in man; assuming that this rate can and will be attained the use of calcium will probably prevent fatal toxic reactions.[3]

2. It has been suggested by Gibbon and co-workers[5] that pulmonary edema is likely to occur when large infusions are given to patients following extensive resection of lung. They present two clinical cases in which they felt that pulmonary edema due to overloading the circulation following extensive lobectomies was the immediate cause of death. This experience led Gibbon and his group to perform a series of well-controlled experiments on cats which tended to substantiate their clinical impression. Similar observations on dogs are the subject of this communication.

We have been interested in the use of massive blood transfusions because we feel that the liberal use of blood to replace operative blood loss has made the radical surgical treatment of certain diseases possible. One striking example is the resection of carcinoma of the esophagus. The operations for removal of the esophagus are long and accompanied

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by considerable blood loss. The liberal use of blood has permitted us to perform these operations without undue haste, and the patients leave the operating room in good condition. Our clinical experience with large blood transfusions in all types of surgery has been presented by Allen and his collaborators.[4] Two of us have made a similar study on patients subjected to thoracic operations.[6] In that study we stated that every cubic centimeter of operative blood loss should be replaced by whole blood. There should be no delay in the replacement of blood loss; shock due to hemorrhage is more easily prevented than treated. The use of large amounts of plasma and glucose or saline solutions does not supply desperately needed red cells and dilute the circulating blood that remains. Data on the cases previously reported are included in Table I. It should be emphasized that when these patients were given large amounts of blood in a short period of time, very little saline or glucose was given in the following twenty-four-hour period. These patients did not develop signs of pulmonary edema or citrate poisoning. When our replacement data are balanced against the measured blood loss for these operations as determined by White and Buxton[7] (1607.5 c.c. average in ten lobectomies, 1,458 c.c. in six pneumonectomies), it is obvious that we have done little more than replace the operative blood loss.

TABLE I

THE CLINICAL USE OF WHOLE BLOOD TRANSFUSIONS IN RESECTION OF LUNG*

OPERATION	NO. OF PT.	OPERATIVE INFUSION	POSTOPERATIVE INFUSION
Lobectomy	14	$942.8 < \frac{500}{2,700}$	782.1
Pneumonectomy	5	$2,060 < \frac{1,300}{2,500}$	630

*Clinical data on patients subjected to lobectomy and pneumonectomy. The figures in the column marked Operative Infusion show the average amount of blood given during operation, as well as the smallest and largest transfusions given. The figures under Postoperative Infusion are the average amount of blood given in the first week postoperatively.

METHOD

Four groups of experiments were carried out.

1. Eight mongrel dogs were subjected to left total pneumonectomy. Upon completion of the operation a transfusion of citrated whole blood in the amount of 15 c.c. per kilogram of body weight was administered into a femoral vein. One cubic centimeter of a 2½ per cent solution of sodium citrate was used as an anticoagulant for every 5 c.c. of blood. All operations were carried out with sterile technique, under intratracheal ether anesthesia. All resection of lung was by dissection technique, using silk ligatures and sutures. Various methods of bronchial closure were employed, but all gave similar results and need not be considered further. Operative blood loss was measured by weighing the sponges. Blood counts were done at intervals when indicated. All animals were observed closely for three days following operation, after

which time studies were discontinued until the dog died or was sacrificed.

2. Eight dogs were subjected to right lower and accessory lobectomy, followed by a transfusion of citrated whole blood in the amount of 15 c.c. per kilogram of body weight. Approximately one month after the first operation the left lower lobe was removed and another transfusion given. All techniques and studies were similar to those in the first group.

3. In twelve dogs the right lower and accessory, and the left lower lobes, were removed at one sitting. Upon completion of the operation a transfusion of citrated whole blood in the amount of 30 c.c. per kilogram of body weight was given into a femoral vein. These animals were subdivided into two groups. In group A we attempted to give the transfusion in ten minutes; actually the transfusion time varied from seven to twelve minutes. The six animals in group B were transfused in from three to six minutes.

4. The fourth experiment was much like those in Group 3. The same operative procedure and transfusion was carried out, the only difference being the addition of bleeding in these animals. Six dogs were bled approximately 25 c.c. per kilogram of body weight, or 50 c.c. less than the amount of the transfusion. A second group of six dogs was bled approximately 20 c.c. per kilogram of body weight or 100 c.c. less than the amount of the transfusion. The bleeding was carried out from a femoral artery, while a transfusion was running into a femoral vein. Studies were similar to those in previous groups.

RESULTS

The results of the first group of experiments are presented in Table II. All animals survived the pneumonectomy and transfusion. The time of infusion varied from one to twenty-three minutes. Three dogs died within one week; one developed an empyema and two succumbed to distemper. There was no clinical or anatomic evidence of pulmo-

TABLE II

LEFT TOTAL PNEUMONECTOMY; CITRATED WHOLE BLOOD TRANSFUSION OF 15 C.C. PER KILOGRAM OF BODY WEIGHT*

DOG NO.	WT. IN KG.	AMT. OF TRANSFUSION (C.C.)	TRANSFUSION TIME (IN MIN.)	PULMONARY EDEMA	TIME OF DEATH	SACRIFICED OR DIED	CAUSE OF DEATH
698	13.0	195	23	–	2 days	S	
702	11.0	165	15	–	5 days	D	Empyema
708	7.7	115.5	15	–	4 days	D	Distemper
716	10.1	151	1	–	5 days	S	
722	9.3	140	5	–	2 weeks	S	
846	12.6	189	15	–	5 days	D	Distemper
850	10.6	158	9	–	2½ weeks	S	
918	10.1	151	5	–	2 weeks	S	

*Data on the eight dogs in Group 1 subjected to left total pneumonectomy, followed by a transfusion of 15 c.c. of blood per kilogram of body weight.

nary edema. Autopsies were performed from two to eighteen days following operation. The operative blood loss averaged 20 c.c. and following transfusion there was a consistent elevation of the red blood count by about 500,000 cells. There was a corresponding increase in hemoglobin and hematocrit.

Table III summarizes the results of the second group. The staged lobectomy was well tolerated. One dog died five days after the second stage with extensive mediastinal and subcutaneous emphysema; two animals succumbed to distemper in five and nine days respectively; one dog was found dead two days after operation, but autopsy failed to reveal any obvious cause of death. Transfusions were given in seven to twenty-six minutes and were not followed by pulmonary edema. A rise in blood counts similar to those in the first group were observed following both operations.

TABLE III

BILATERAL LOBECTOMY (SECOND STAGE); CITRATED WHOLE BLOOD TRANSFUSION OF 15 C.C. PER KILOGRAM OF BODY WEIGHT WITH EACH TRANSFUSION*

DOG NO.	WT. IN KG.	AMT. OF TRANSFUSION (C.C.)	TRANSFUSION TIME (IN MIN.)	PULMONARY EDEMA	TIME OF DEATH	SACRIFICED OR DIED	CAUSE OF DEATH
742	15.2	228.0	26	–	5 days	D	Emphysema
	14.9	223.0	20	–			
709	10.2	153.0	20	–	2 months	S	
	10.1	151.5	20	–			
803	11.6	174.0	11	–	2 days	D	Not known
	12.2	183.0	15	–			
806	10.1	151.5	7	–	6 weeks	S	
	10.1	151.5	10	–			
813	17.2	258.0	22	–	6 weeks	S	
	15.4	231.0	10	–			
817	12.1	181.0	11	–	5 days	D	Distemper
	11.2	168.0	12	–			
839	12.0	180.0	13	–	9 days	D	Distemper
	12.4	186.0	8	–			
909	11.0	165.0	10	–	1 week	S	
	13.0	195.0	7	–			

*Tabulated data on the eight dogs in Group 2 undergoing a staged bilateral lobectomy. The operations were done approximately one month apart, and each operation was followed by a transfusion of 15 c.c. of blood per kilogram. The top line of figures for each animal are for the right lower and accessory lobectomy; the bottom line represents the second stage, the left lower lobectomy.

The results in the third group of dogs are tabulated in Table IV. For convenience we have divided this experiment into groups A and B, depending on the transfusion time. In group A a transfusion of 30 c.c. per kilogram of body weight was given in seven to twelve minutes following removal of the accessory and both lower lobes at one sitting. This rather vigorous experiment was attempted because we had been unable to produce pulmonary edema as yet. Four of these animals died in from two days to two weeks following operation

TABLE IV

BILATERAL LOBECTOMY (FIRST STAGE); CITRATED WHOLE BLOOD TRANSFUSION OF 30 C.C. PER KILOGRAM OF BODY WEIGHT*

GROUP	DOG NO.	WT. IN KG.	AMT. OF TRANSFUSION (C.C.)	TRANSFUSION TIME (IN MIN.)	PULMONARY EDEMA	TIME OF DEATH	SACRIFICED OR DIED	CAUSE OF DEATH
A	847	10.3	306.0	10	–	2 days	D	Hemorrhage of femoral vein
	848	11.0	330.0	9	–	10 days	D	Empyema
	849	14.0	420.0	12	–	2 weeks	D	Distemper
	863	10.5	315.0	9	–	2 days	D	Distemper
	864	12.9	387.0	10	–	5 weeks	S	
	900	8.0	240.0	7	–	2½ months	S	
B	914	8.6	258.0	5	–	2½ months	S	
	928	9.7	291.0	3	+	1 day	D	Intrapleural hemorrhage
	935	9.3	279.0	6	+	1 day	D	Pulmonary edema
	941	12.8	384.0	5	+	2 days	D	Pulmonary edema
	942	8.4	252.0	6	+	2 days	D	Pulmonary edema
	962	7.4	222.0	3	+	1 day	D	Pulmonary edema

*Results in the twelve animals in Group 3, which is divided into subgroups A and B. In both groups the lower and accessory lobes were removed at one sitting, and the operation was followed by a transfusion of 30 c.c. per kilogram of body weight. In group A the transfusion was given in seven to twelve minutes; the animals in group B were transfused in three to six minutes. Note that edema occurred only in the second group.

TABLE V

BILATERAL LOBECTOMY (ONE STAGE), TRANSFUSION AND BLEEDING*

GROUP	DOG NO.	WT. IN KG.	AMT. OF TRANSFUSION (C.C.)	AMT. OF BLEEDING (C.C.)	TRANSFUSION TIME (IN MIN.)	PULMONARY EDEMA	TIME OF DEATH	SACRIFICED OR DIED	CAUSE OF DEATH
A	960	9.8	294	244	5.5	–	2 days	D	Emphysema pneumothorax
	958	8.6	264	214	5.0	–	5 days	D	Empyema
	963	8.0	240	190	6.0	–	9 days	D	Distemper
	911	8.8	264	214	5.0	–	2 days	D	Distemper
	917	13.4	402	352	7.0	–	8 days	D	Hemorrhage from leg wound
	946	9.4	282	232	5.0	+	1 day	D	Pulmonary edema and emphysema
B	1,000	11.1	333	222	7.0	–	7 days	D	Emphysema
	535	11.6	348	248	7.0	+	1 day	D	Pulmonary edema
	5	9.5	285	185	10.0	–	3 weeks	S	
	4	11.7	350	250	6.5	–	3 weeks	S	
	35	8.8	264	164	6.5	+	1 day	D	Pulmonary edema
	6	15.0	450	350	7	–	4 days	D	Distemper

*Tabulated results in Group 4. All animals were subjected to one-stage bilateral lobectomy and transfusion. In addition the animals in group A were bled 25 c.c. per kilogram, while those in group B were bled 20 c.c. per kilogram.

of various causes, but none developed pulmonary edema. Microscopic sections showed congestion of pulmonary vessels, but no edema. The rise in blood count was marked, occasionally being as much as 1,000,000 red blood cells. The transfusions in the six dogs in group B were given in three to six minutes. Five of the six animals developed pul-

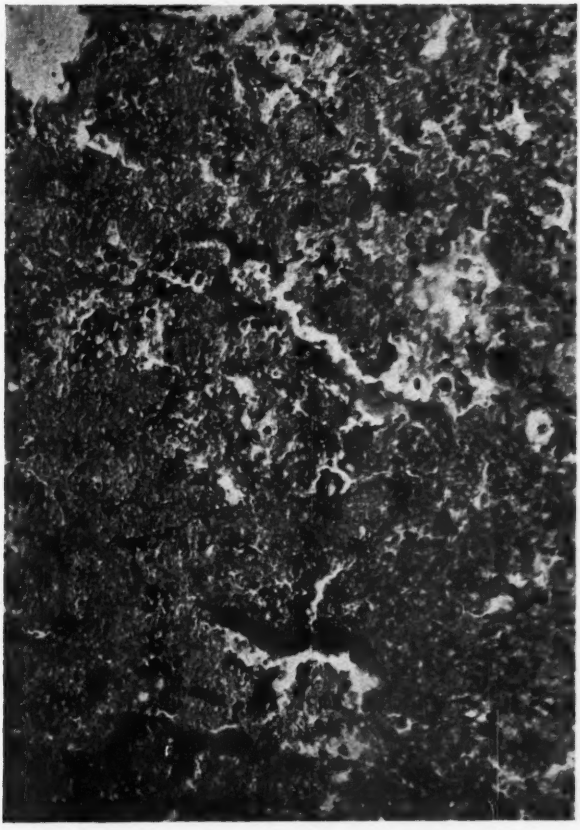

Fig. 1.—Photomicrograph of a section of lung from Dog 942; this animal died two days following bilateral lung resection and transfusion of 30 c.c. of whole blood per kilogram of body weight. There is marked congestion of the pulmonary capillaries, and considerable edema fluid in the alveolar spaces.

monary edema causing death in one to two days. At autopsy the trachea was full of bloody froth, and thin blood-tinged fluid escaped from the cut surface of the lung on sectioning. The lungs were heavy, soggy, and deep red in color. Microscopic sections revealed extensive edema fluid in the alveolar spaces (Fig. 1).

The results in the fourth group are given in Table V. The plan of this experiment was to bleed the dogs so that overtransfusion would be avoided. Since the measured blood loss in pneumonectomy in dogs

averaged only 20 c.c. we felt that not more than 50 c.c. of blood would be lost in the bilateral lobectomy operation. The dogs in group A were therefore bled 25 c.c. per kilogram of body weight or 50 c.c. less than the total transfusion. Only one animal developed pulmonary edema. In group B the bleeding was 100 c.c. less than the transfusion. Two dogs developed pulmonary edema. All transfusions were given in less than ten minutes. Blood counts remained constant within the range of experimental error. The bleeding could have been omitted and transfusions of 50 and 100 c.c. given, but the bleeding and transfusion tends to simulate operative blood loss and replacement.

In the discussion of animal experimentation that tends to simulate clinical practice one must avoid applying data obtained from dogs directly to human physiology. In addition to the basic differences between human and dog physiology, certain conditions peculiar to this experiment must be considered. Our conclusions, therefore, must be made with four factors in mind.

1. Blood loss in dog surgery is minimal compared to hemorrhage in similar operations on patients. The measured blood loss for lobectomy and pneumonectomy in our animals was, on the average, 20 c.c. All animals except those in Group 4 were overtransfused; this is confirmed by the elevation in blood counts postoperatively.

2. These experiments, except in the case of pneumonectomy, are unusually rigorous. Clinically bilateral resection of the lung is done at staged operations, at intervals of several months, and in some cases, years. The amount of blood given was not excessive: 15 to 30 c.c. per kilogram of body weight correspond to 1,050 to 2,100 c.c. of blood in a 70 kilogram man. However, this amount of blood was given in a very short time.

3. The remaining lobes in dogs are normal; frequently in clinical suppurative disease of the lung the remaining upper lobes contain residual disease.

4. We have no accurate measurement of the degree, if any, of edema that occurred in animals who survived. Almost surely some of these dogs developed a moderate amount of edema and survived. Moist rattling breathing was observed in some of the dogs who died with edema, but in none who survived. Biopsy of the lung in the first or second days following the operation and transfusion was considered, but felt to be too hazardous to undertake. Venous pressure measurements were not done, for the reason that elevation of the pressure would not necessarily indicate edema.

Certain factors, however, are quite evident. Gibbon has shown that after resection of the lung, animals do not tolerate large transfusions as well as normal animals, and pulmonary edema is prone to occur. With the increasing need for massive transfusions of whole blood, it is

necessary to establish a range of safety. We believe that three factors are present in addition to the amount of lung resected.

1. Obviously the amount of blood given will determine partially whether edema develops. None of the animals given 15 c.c. of blood per kilogram developed edema, although in one instance the transfusion was given in one minute. Animals given 30 c.c. per kilogram developed edema quite frequently.

2. The time of administration is extremely important, at least experimentally. We were not able to produce edema unless the transfusion was given very rapidly. In Group 3 no edema was observed in dogs transfused in seven to twelve minutes; however, if the same transfusion was given in three to six minutes, five of six dogs died of pulmonary edema. Clinically this may not be an important factor, since blood is given at a considerably slower rate in most instances.

3. Overtransfusion tends to promote edema. The experiments in Group 4 were identical to those in Group 3 B except for the addition of bleeding. The bleeding and the operative blood loss approximated the tranfusion. Pulmonary edema occurred much less frequently in animals subjected to bleeding. This may be the most important clinical factor. If a transfusion, no matter how large, is given to replace hemorrhage, in a reasonable period of time, or simultaneously with the hemorrhage, pulmonary edema probably will not occur except in the presence of severe cardiovascular or pulmonary disease. In actual practice one of two things is likely to happen. When a patient sustains a severe hemorrhage whole blood may not be available for immediate replacement. Usually large amounts of saline, glucose, or plasma are administered until blood is obtained. If no intravenous therapy is given, fluid from the extravascular tissues enters the blood

TABLE VI

SUMMARY*

GROUP	OPERATION	TRANSFUSION (AMT. IN C.C. PER KG. BODY WEIGHT)	DOGS	PULMONARY EDEMA
1	Pneumonectomy	15	8	0
2	Bilateral lobectomy (2 stage)	15	8	0
3	Bilateral lobectomy (1 stage)	30		
	A. Transfusion time 7 to 12 min.		6	0
	B. Transfusion time 3 to 6 min.		6	5
4	Bilateral lobectomy (1 stage)	30		
	A. Bled 25 c.c. per Kg. and transfused in 5 to 7 min.		6	1
	B. Bled 20 c.c. per Kg. and transfused in 5 to 7 min.		6	2

*The results of all four experimental groups are summarized with respect to the severity of the operation, the amount and time of transfusion, and the occurrence of pulmonary edema.

stream. If then, a few hours later, blood is obtained and given in the amount of the hemorrhage the circulatory system is overloaded, the heart may fail, and edema of the lungs occur. It is not a matter solely of how much blood is given because any fluid in sufficient amount will eventually overload the heart. We do not wish to condemn the use of blood substitutes in the treatment of shock due to hemorrhage, but if large amounts of these solutions are given, one must necessarily limit the volume of whole blood given. With the wide adoption of blood banks.there is little excuse, in civilian surgery at least, for failure to use whole blood under such circumstances.

An interesting observation, unrelated to the primary study, was made in the course of the experiments. A total of thirty-two dogs was subjected to removal of the accessory and both lower lobes. Four of these animals died of mediastinal emphysema. All developed extensive subcutaneous emphysema and one had a bilateral pneumothorax. The overexpansion of the upper lobes after the extensive resection of lung resulted in rupture of alveoli allowing air to dissect back along the bronchovascular sheaths to the mediastinum. Compression of mediastinal structures or pneumothorax resulted in death.

SUMMARY AND CONCLUSIONS

1. Clinical and experimental data are presented to demonstrate that massive whole blood transfusions following extensive lung resection are well tolerated, if certain precautions are observed.

2. Three factors were demonstrated experimentally in the production of pulmonary edema, namely, the amount of lung resection, the rate of infusion, and the amount of infusion. No edema was observed in experiments simulating clinical practice.

3. By decreasing the rate and the amount of overtransfusion, the incidence of pulmonary edema following one-stage bilateral lung resection was considerably reduced.

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DISCUSSION

DR. DERYL HART, Durham, N. C.—I so thoroughly agree with this paper that I want to add what little I can to it. I might say that in each of the cases presented in the discussion of pneumonectomies we gave anywhere from 500 to 2,500 c.c. of blood during the operation. In each there were many adhesions and great loss of blood, with long operative procedures. In the presence of the great loss of blood which could be stopped only by packing, these patients were taken off the operating table in relatively good condition, since there was adequate blood and fluid replacement.

We tried to regulate the inflow of blood to replace all losses and thus maintain the blood pressure. If there was little loss of blood, plasma to keep up the blood volume was at times given rather than whole blood. So far I have not seen any complications from giving these large quantities of blood. We follow the same course with other types of surgery. In one patient with a gastric hemorrhage we gave 3,000 c.c. of blood within twelve to eighteen hours before beginning a gastric resection. An additional 500 c.c. of blood were given during the operation. Convalescence was complicated only by an acute parotitis.

The largest amount of blood per pound of body weight given by us was to a poorly nourished 6-year-old patient during the removal of a large solid and cystic infected intra-abdominal teratoma. Fifteen hundred cubic centimeters of whole blood were given during the three- to four-hour operation. The patient made a satisfactory convalescence.

Regarding the recent remark reflecting on the accuracy of the reported low infection rate given in my discussion of the papers on pneumonectomies, the statistics quoted were from the North Carolina State Sanatorium, and were reported to me by the doctors of that institution. I do not doubt them since our experience had already shown similar results in almost eliminating infections in clean operative wounds. Most of the interns on my staff never see an infection in a clean wound of any type during the entire year. We feel that today in the well-run operating room with otherwise good surgical technique, air contamination is the greatest source of danger in so far as infection of clean operative wounds is concerned.

We will be glad to have anyone at any time check on our patients both for postoperative wound infections and for postoperative temperature elevations. Our surgery has been so truly revolutionized by eliminating most of the air-borne wound contaminants that when a patient has a postoperative temperature elevation the first reaction of the doctor is that it cannot be in the wound, so extremely rare is such a complication. This statement will be verified by medical students who have worked on the surgery division as well as by the surgical staff (both resident and attending) of the Duke Hospital.

DR. FRANK S. DOLLEY, Los Angeles, Calif.—I would like to add a word to this most timely paper in regard to the great desirability of having whole blood on hand when an operation of any magnitude whatever is undertaken. It is our routine, as no doubt it is with almost all of you, to start an intravenous saline solution at the beginning of all major thoracic operations. In the hospitals where we usually operate blood is at hand so that within three or four minutes it can be introduced into the blood stream. At other institutions, because we did not have sufficient blood at once available during the course of the operation, disasters occurred in three cases that might otherwise have been averted.

As Dr. Thornton said, it is so much better to replace the blood when it is needed than to try to counteract some natural metabolic readjustment that the body itself develops in the attempt to replace it.

DR. DAVID H. WATERMAN, Knoxville, Tenn.—Dr. Thornton did not mention the operation of thoracoplasty, and I think we might dwell briefly on that. I believe it is becoming routine in most clinics to transfuse patients during thoracoplasty. In my own personally operated series I have always given during each stage a transfusion of at least 500 c.c., as well as glucose in saline, via a Lindemann needle already in place, and have never seen a patient who had not been benefited. If we have in mind Dr. Thornton's principles of replacing blood loss, every patient profits by the administration of blood at the time it is being lost.

Shock is almost unknown when this is done, granted careful anesthesia and techniques are followed, and I think results well warrant its use.